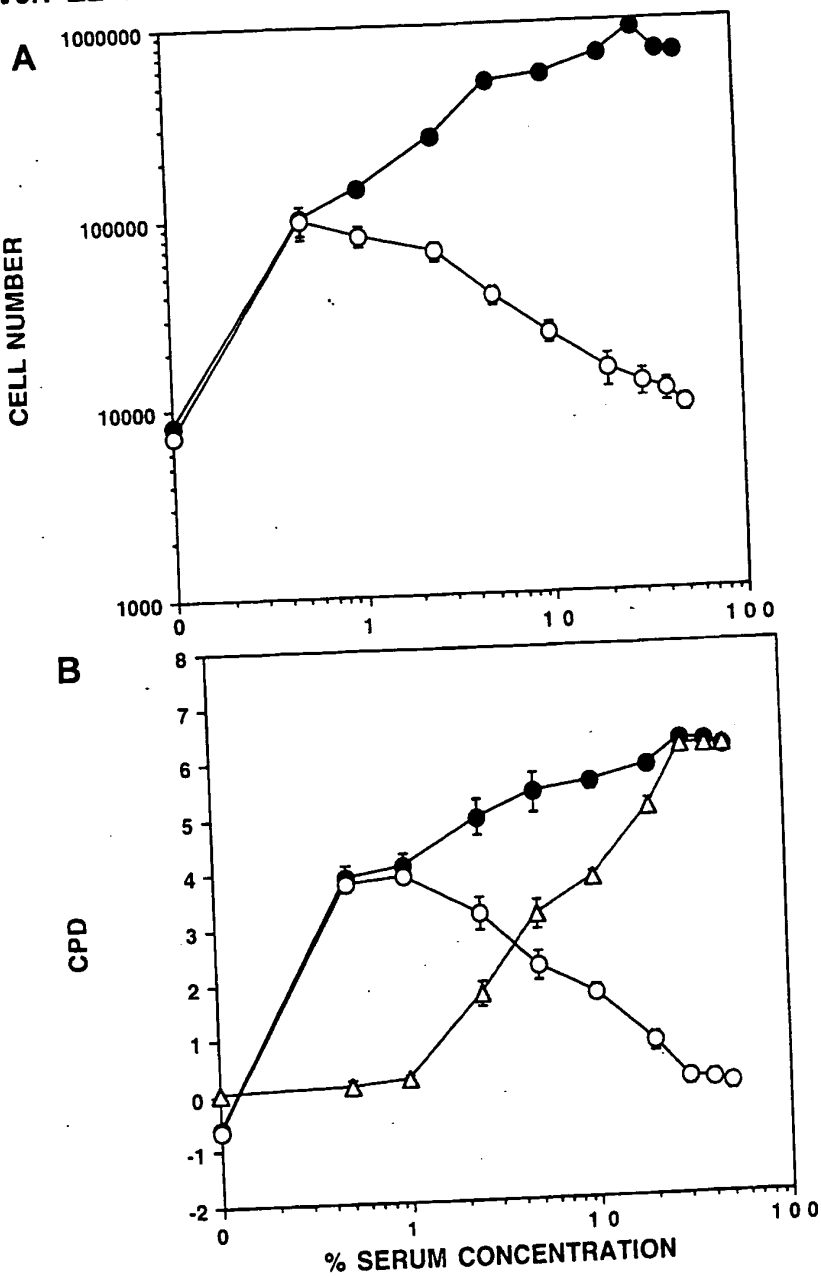
FIGURE 1

MTW9/PL2 CELL GROWTH IN 50% CDE - HORSE SERUM

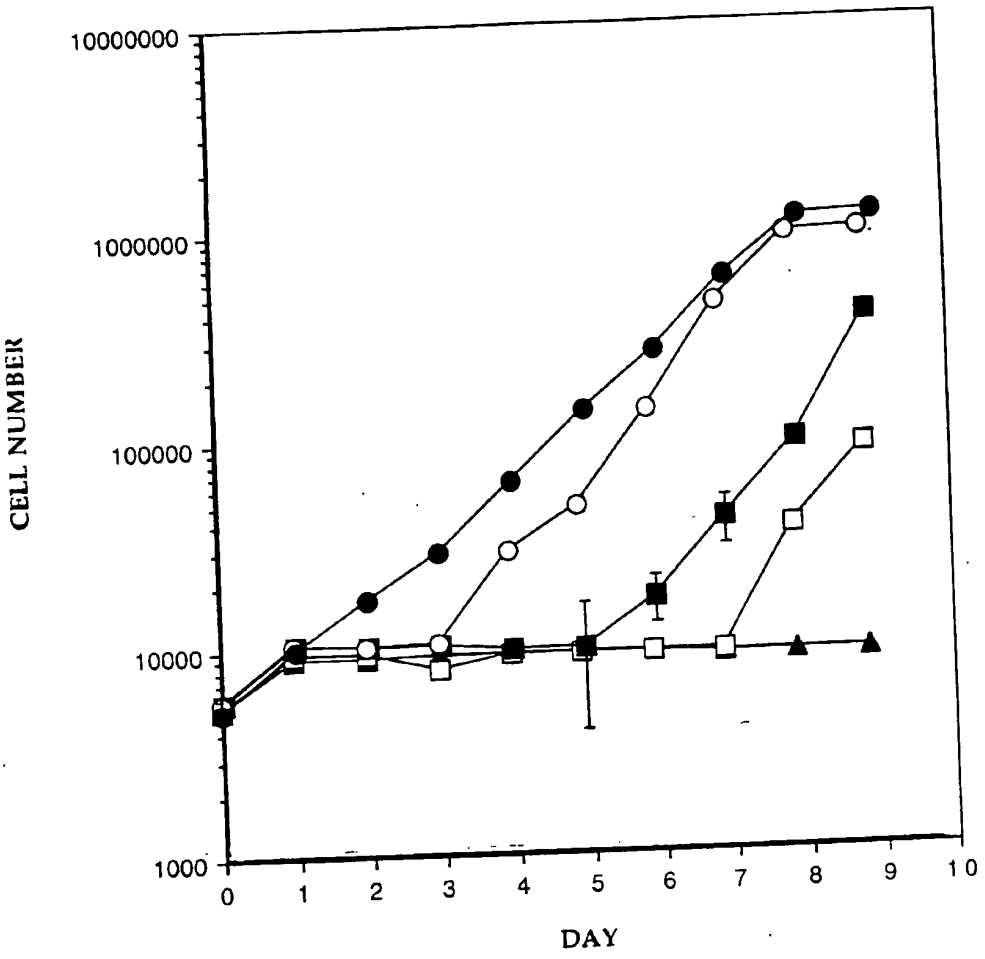


A: DATA EXPRESSED AS CELL NUMBER AFTER 7 DAYS
Growth with 1.0×10^{-8} M E_2 (closed circles) and without hormone (open circles) in medium containing the designated concentrations of serum.

B. DATA IN (A) EXPRESSED AS CPD
The symbols indicate the same conditions as (A) except the open triangles show CPD differences between growth in dishes with and without the hormone (Difference = estrogenic effect on growth).

FIGURE 2

MTW9/PL2 CELL GROWTH IN 50% CDE - HORSE SERUM WITH ESTROGENS ADDED AT VARIOUS TIMES AFTER SEEDING

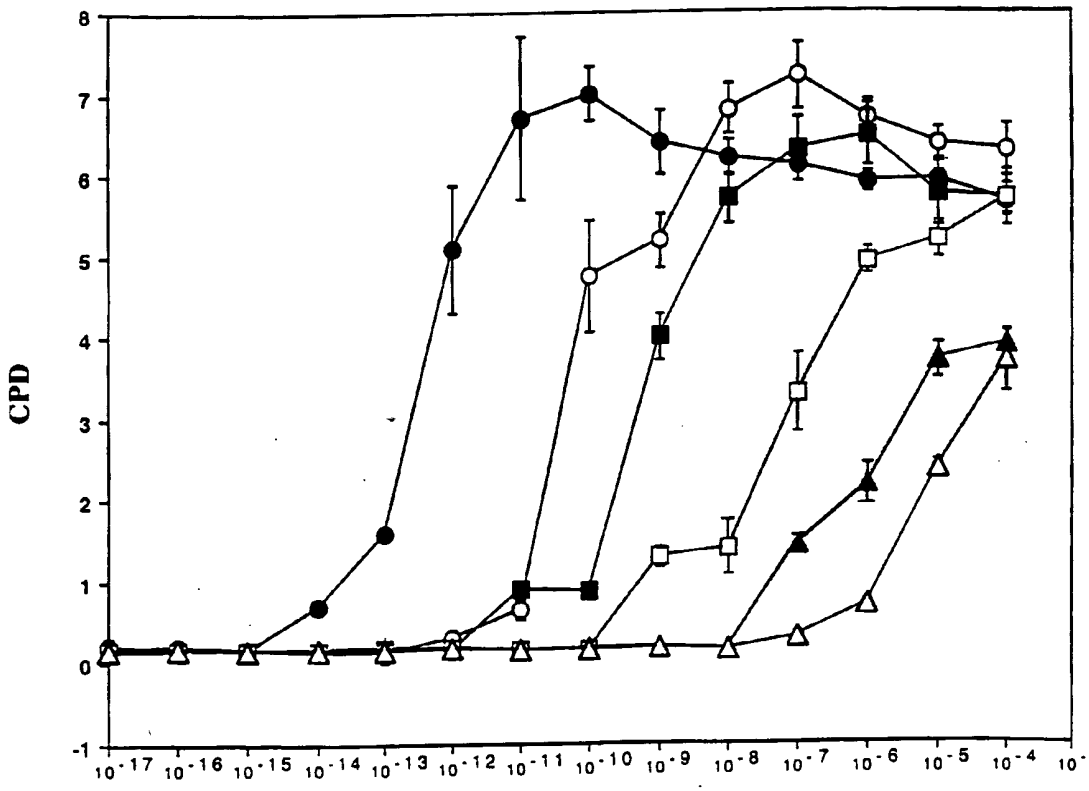


LEGEND:

Control growth in the absence of exogenous estrogen is shown by (triangles). In other dishes, 1.0 x 10^{-8} M E_2 was added at the beginning of the experiment (closed circles), after 48 h (open circles), after 96 h (closed squares), or after 144 h (open squares).

FIGURE 3

STEROID HORMONE DOSE RESPONSE EFFECTS WITH MTW9/PL2 CELLS IN 50% CDE - HORSE SERUM

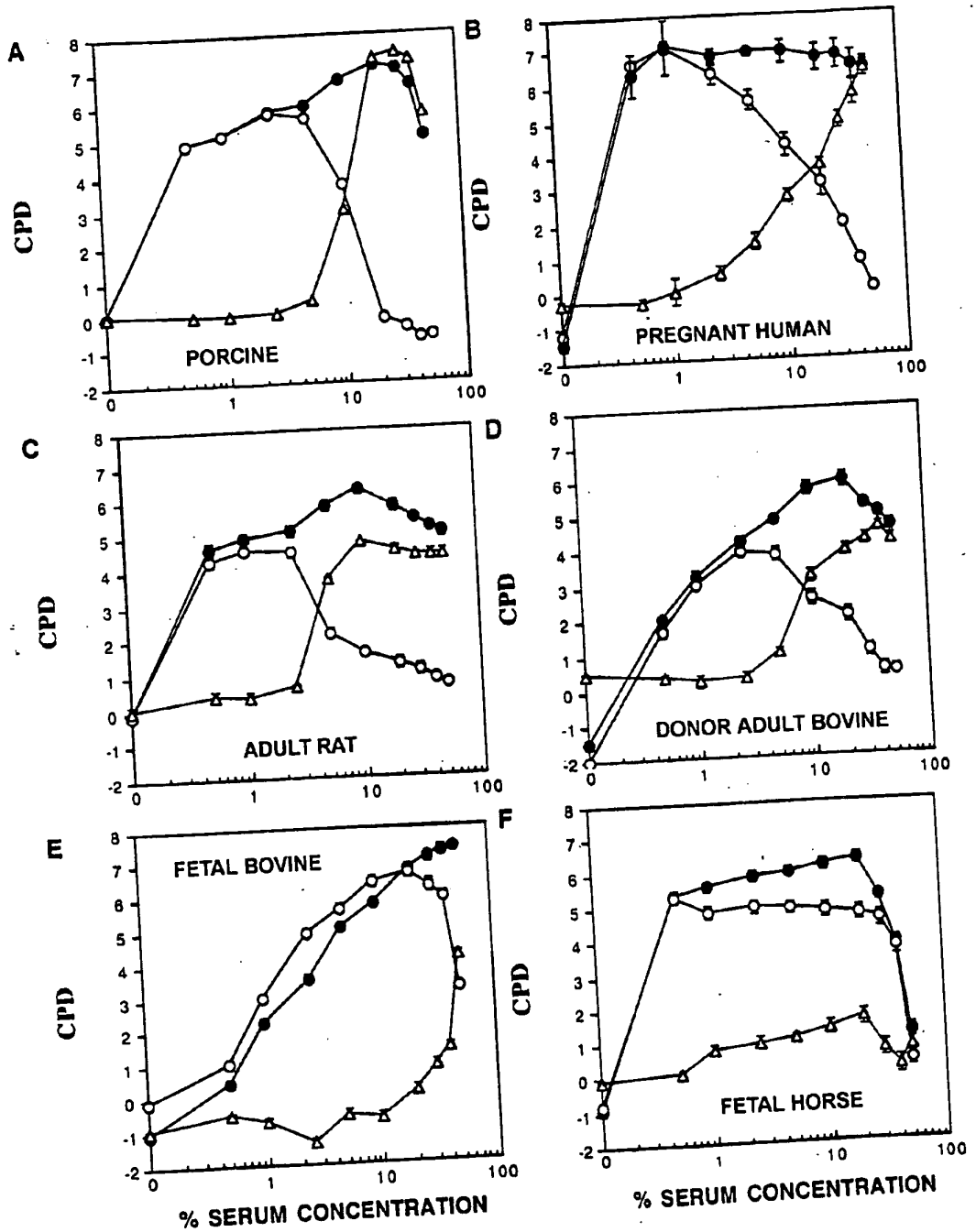


LEGEND:

Closed circles = E_2
Open circles = E_1
Closed squares = E_3
Open squares = Progesterone
Closed triangles = DHT
Open triangles = T

FIGURE 4

MTW9PL2 CELL GROWTH IN CDE SERUM FROM DIFFERENT SPECIES



LEGEND: Open circles = $-E_2$
Closed circles = $+E_2$
Open triangles = Estrogenic effect

FIGURE 5

CDE HORSE SERUM TITRATION
GH4C1 CELLS

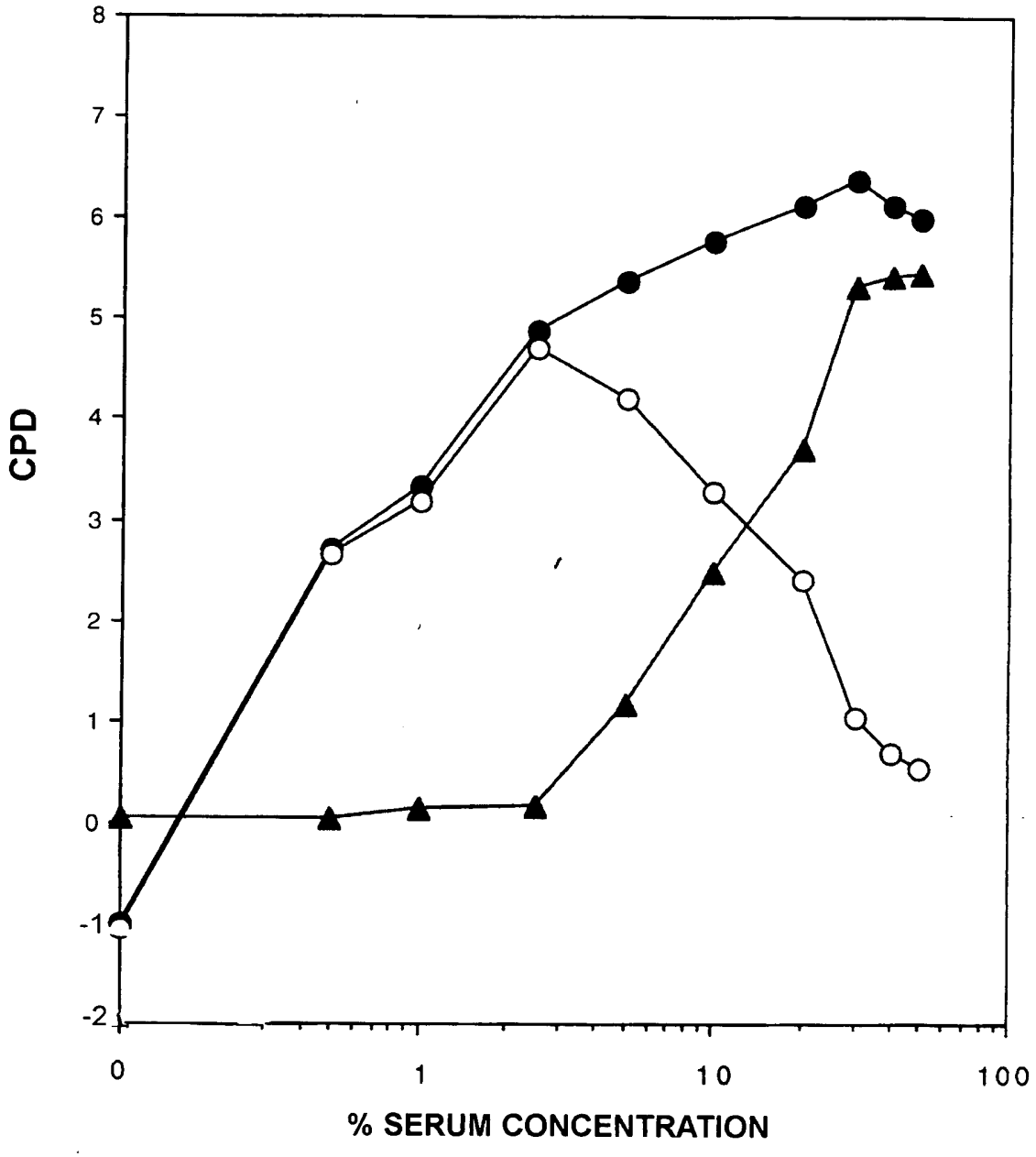
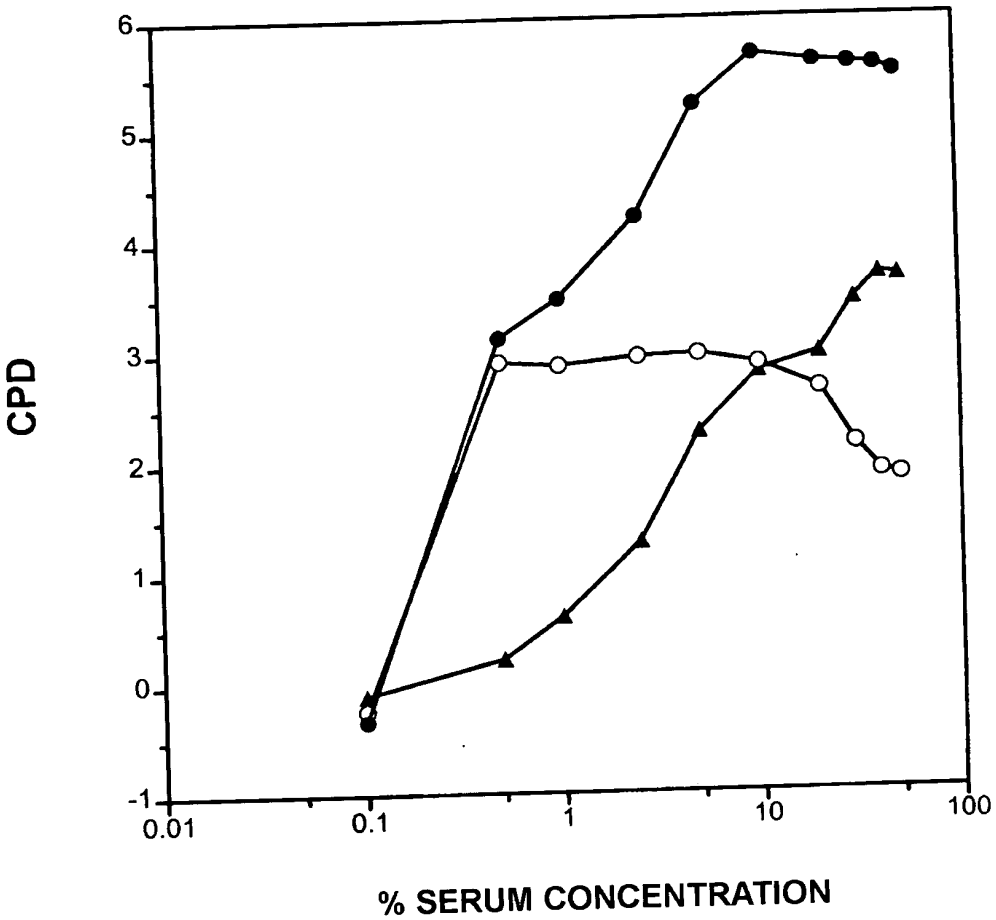


FIGURE 6

ZR-75-1 CELLS IN CDE - HORSE SERUM ± 10 nM E_2

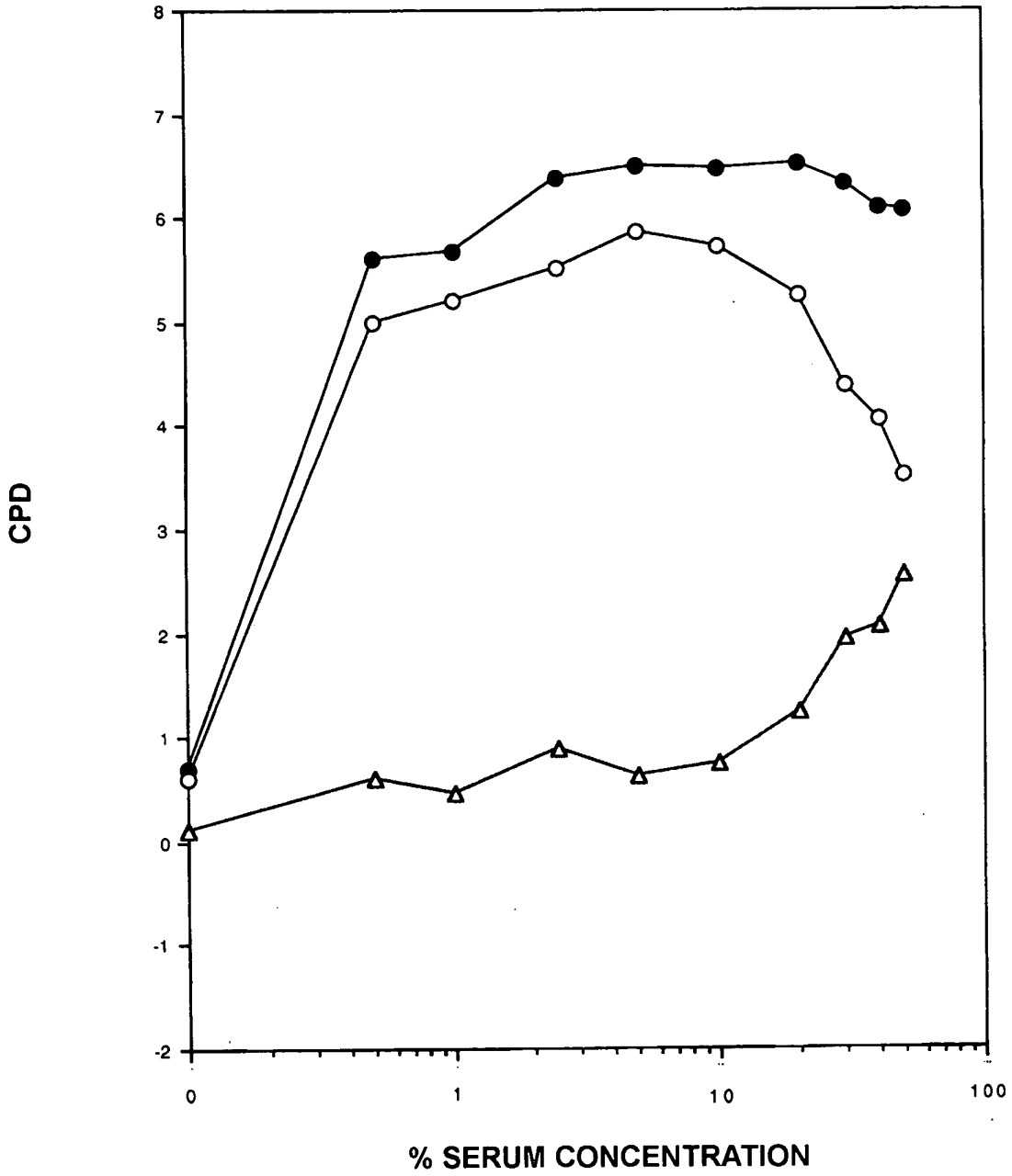


LEGEND:

Closed circles = $+E_2$
Open circles = $-E_2$
Closed triangles = Estrogenic effect

FIGURE 7

MCF7A CELL GROWTH IN CDE - HORSE SERUM $\pm E_2$

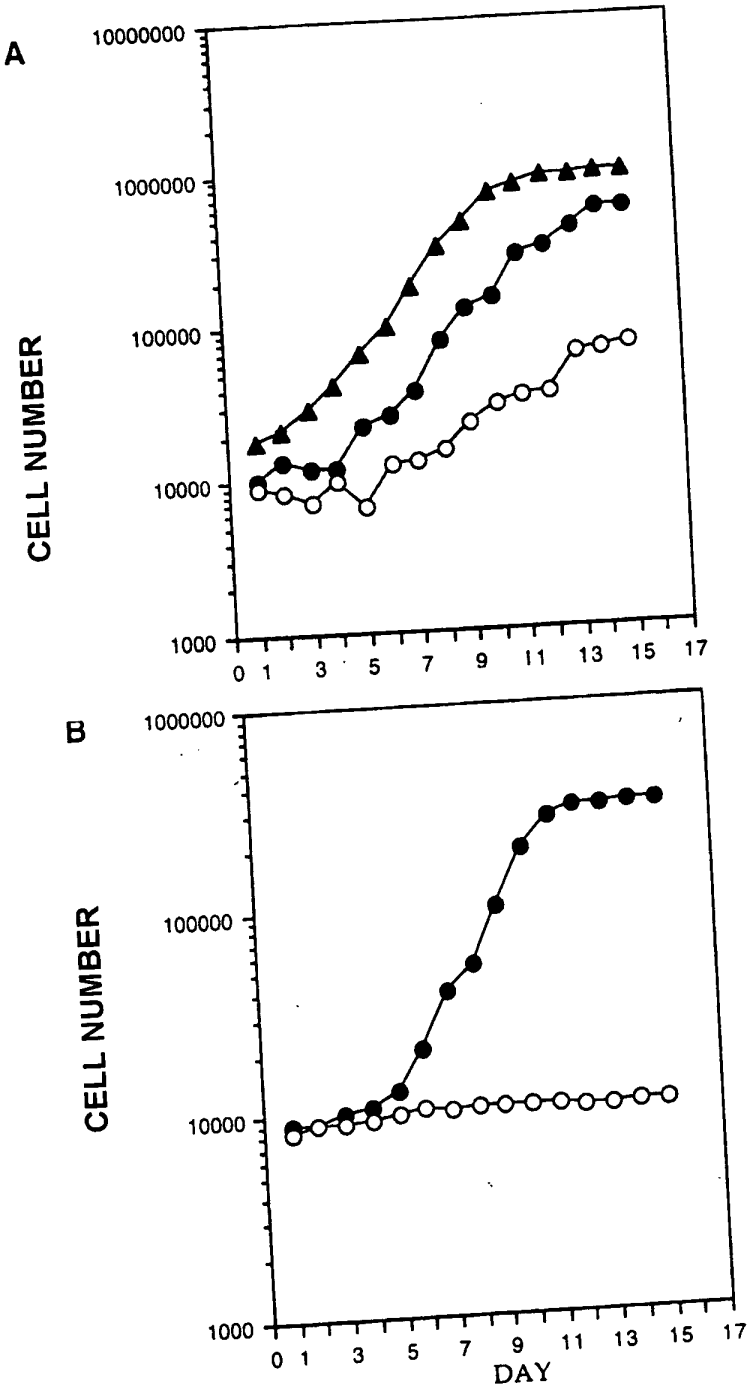


LEGEND:

Closed circles = $+E_2$
Open circles = $-E_2$
Closed triangles = Estrogenic effect

FIGURE 8

GROWTH KINETICS OF T47D HUMAN BREAST CANCER CELLS IN CDE - HORSE SERUM ±10 nM E_2

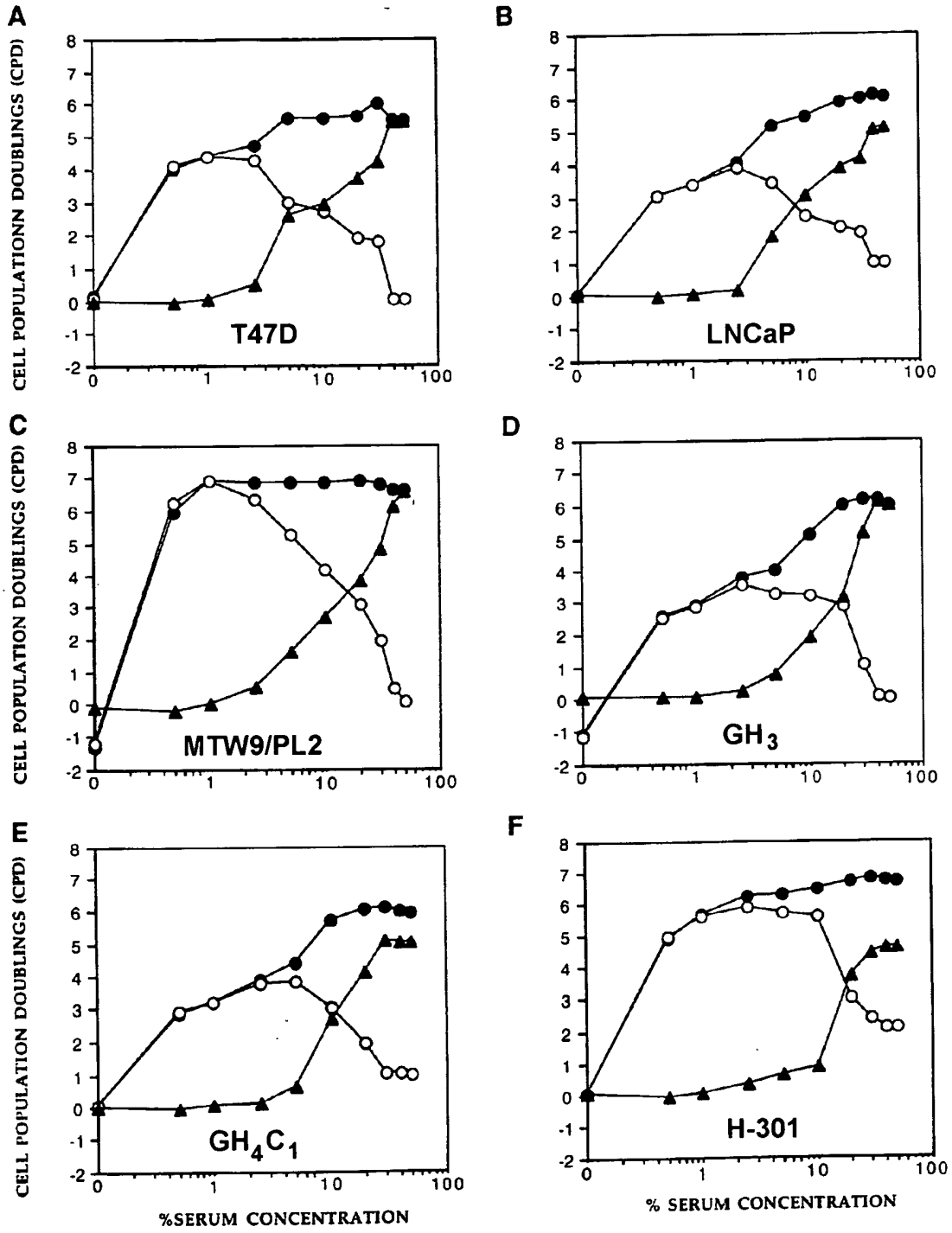


(A) The growth of the cells in medium with 20% (v/v) serum with 10 nM E_2 (closed circles) and without the steroid (open circles). As comparison, growth is shown in medium containing 10% (v/v) FBS (triangles).

(B) T47D cell growth kinetics in medium with 50% (v/v) serum with E_2 (closed circles) and without the steroid (open circles).

FIGURE 9

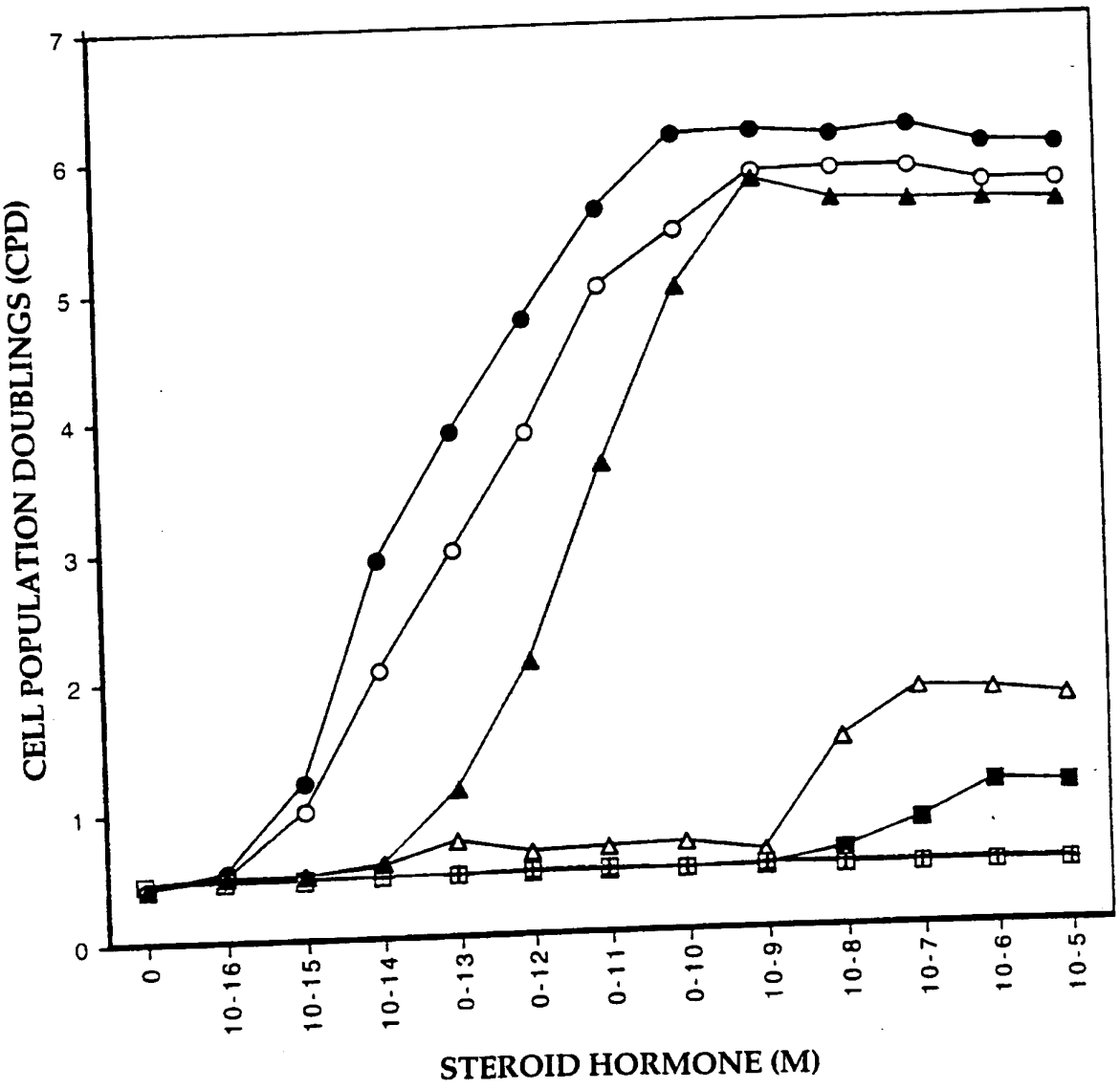
GROWTH OF HUMAN & RODENT CELL LINES IN 50% CDE - HORSE SERUM $\pm E_2$ (10 nM)



LEGEND: Closed circles = Medium with 10 nM E_2
Open circles = Medium without E_2
Triangles = Estrogenic effect

FIGURE 10

DOSE RESPONSE OF STEROID HORMONES WITH T47D CELLS IN 50% CDE - HORSE SERUM

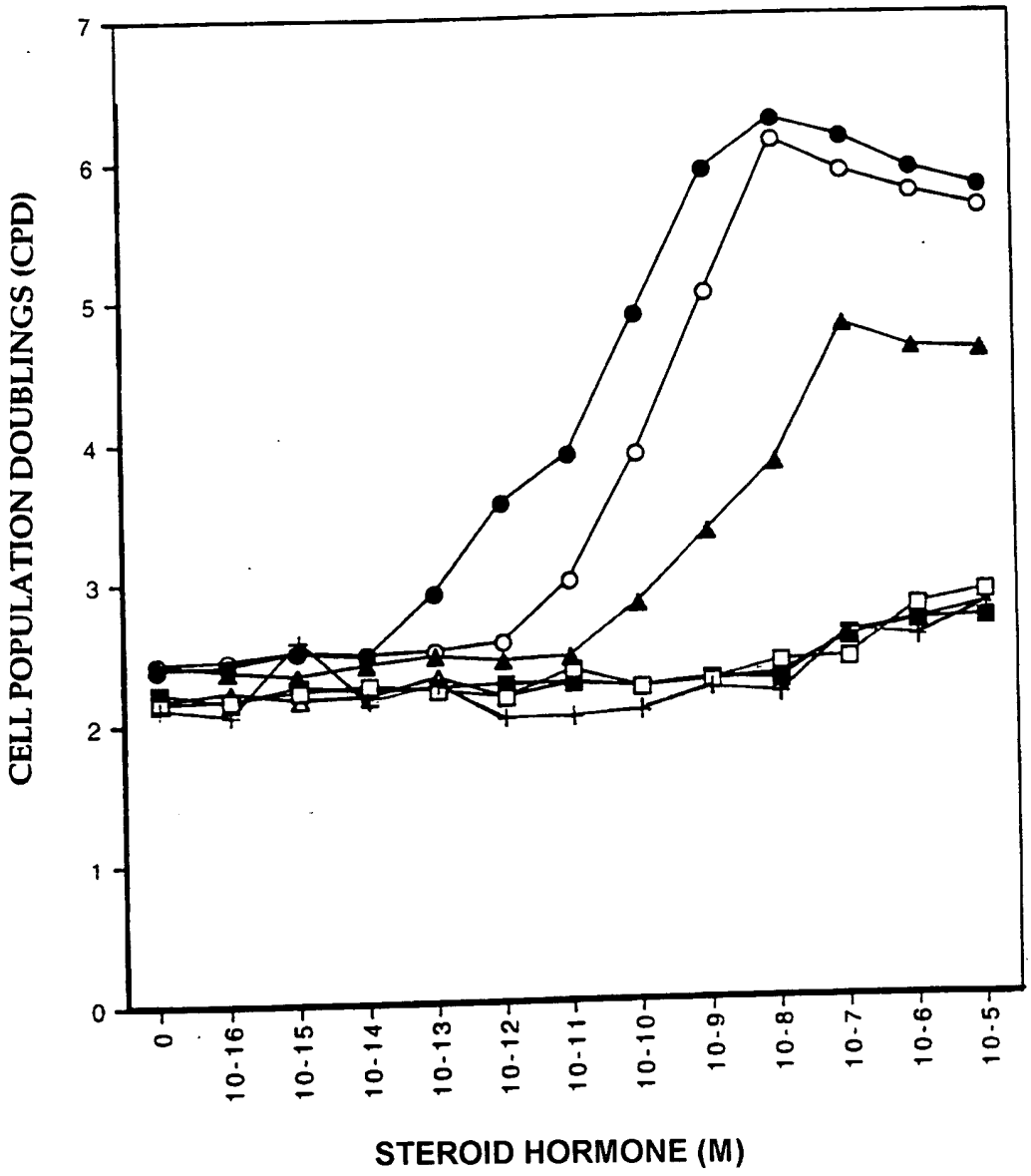


LEGEND:

Growth after 14 days is shown in response to:
Closed circles = E_2
Open circles = E_1
Closed triangl s = E_3
Open triangles = DHT
Closed squares = Testosterone
Open squares = Progesteron
Crosses = Cortisol

FIGURE 11

DOSE RESPONSE OF STEROID HORMONES WITH H-301 CELLS IN 50% CDE - HORSE SERUM



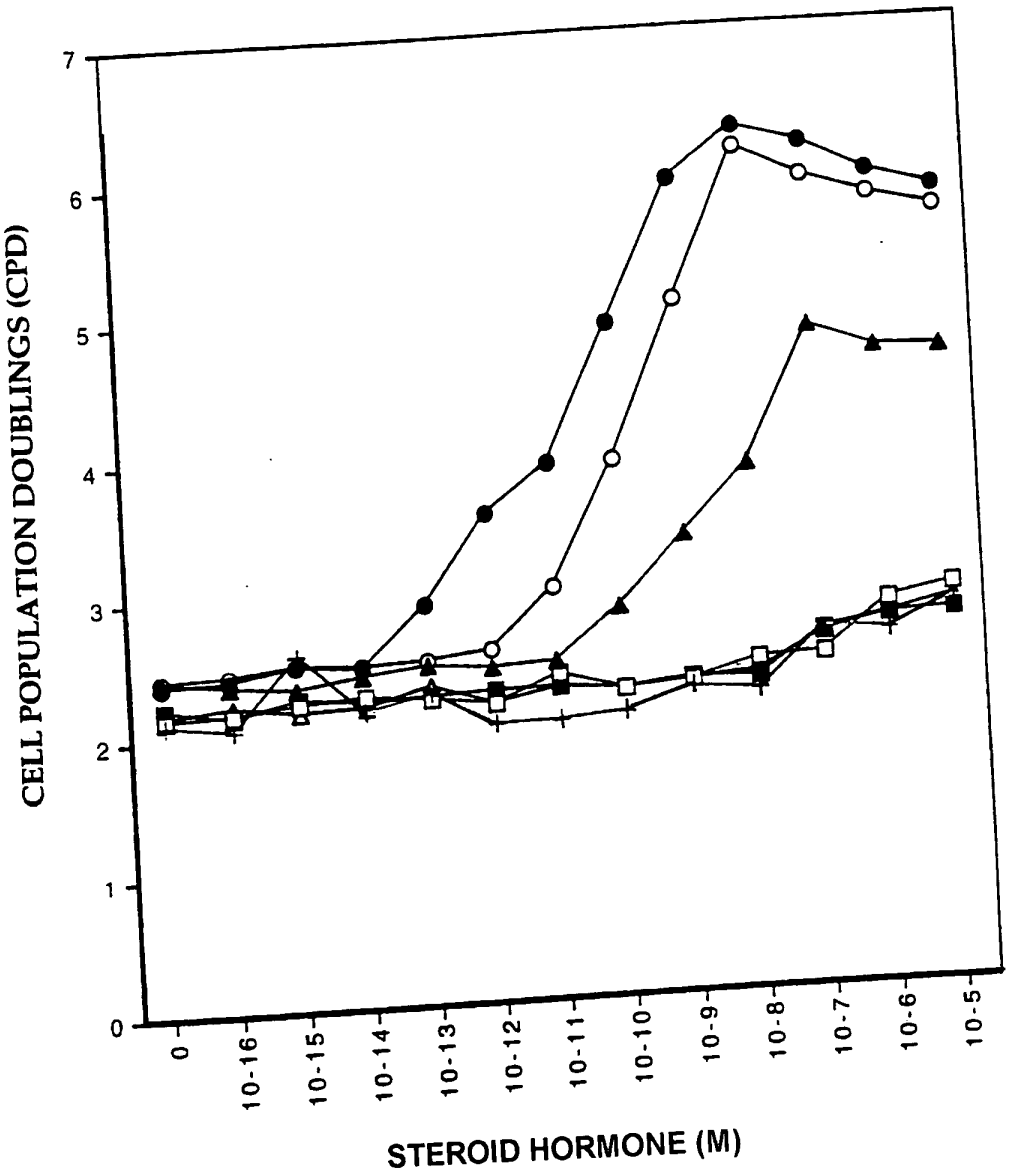
LEGEND:

Growth after 9 days is shown in response to:

- **Closed circles = E_2**
- **Open circles = E_1**
- **Closed triangles = E_3**
- **Open triangles = DHT**
- **Closed squares = Testosterone**
- **Open squares = Progesterone**
- **Crosses = Cortisol**

FIGURE 12

DOSE RESPONSE OF STEROID HORMONES WITH H-301 CELLS IN 50% CDE - HORSE SERUM

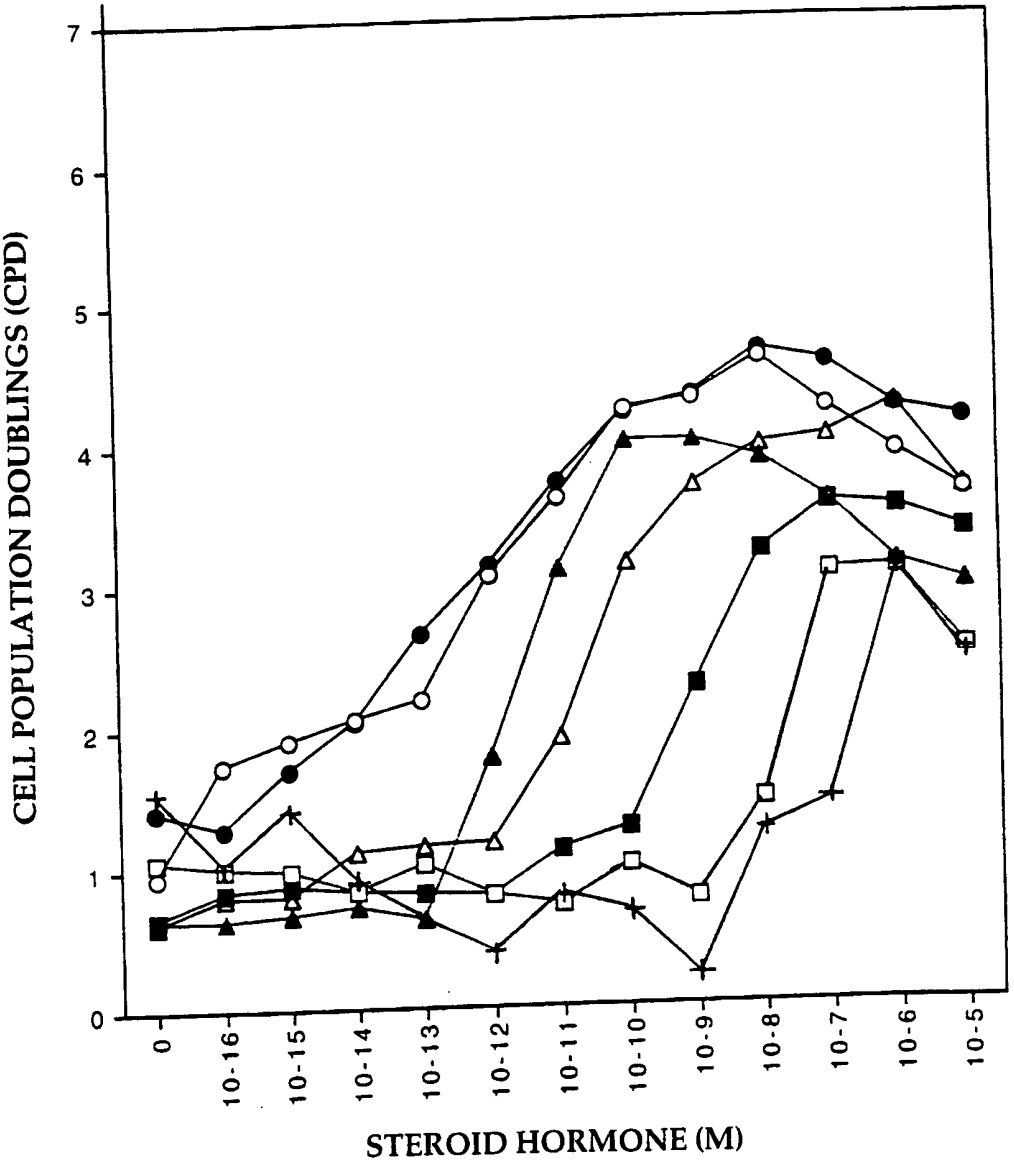


LEGEND:

Growth after 9 days is shown in response to:
Closed circles = E_2
Open circles = E_1
Closed triangles = E_3
Open triangles = DHT
Closed squares = Testosterone
Open squares = Progesterone
Crosses = Cortisol

FIGURE 13

DOSE RESPONSE OF STEROID HORMONES WITH LNCaP CELLS IN 50% CDE - HORSE SERUM



LEGEND:

Growth after 14 days is shown in response to:
Closed circles = E_2
Open triangles = E_1
Open squares = E_3
Open circles = DHT
Closed triangles = Testosterone
Closed squares = Progesterone
Crosses = Cortisol

FIGURE 14

T_3 TITRATION OF GH_3 CELLS GROWN IN SERUM - FREE MEDIUM (PCM)

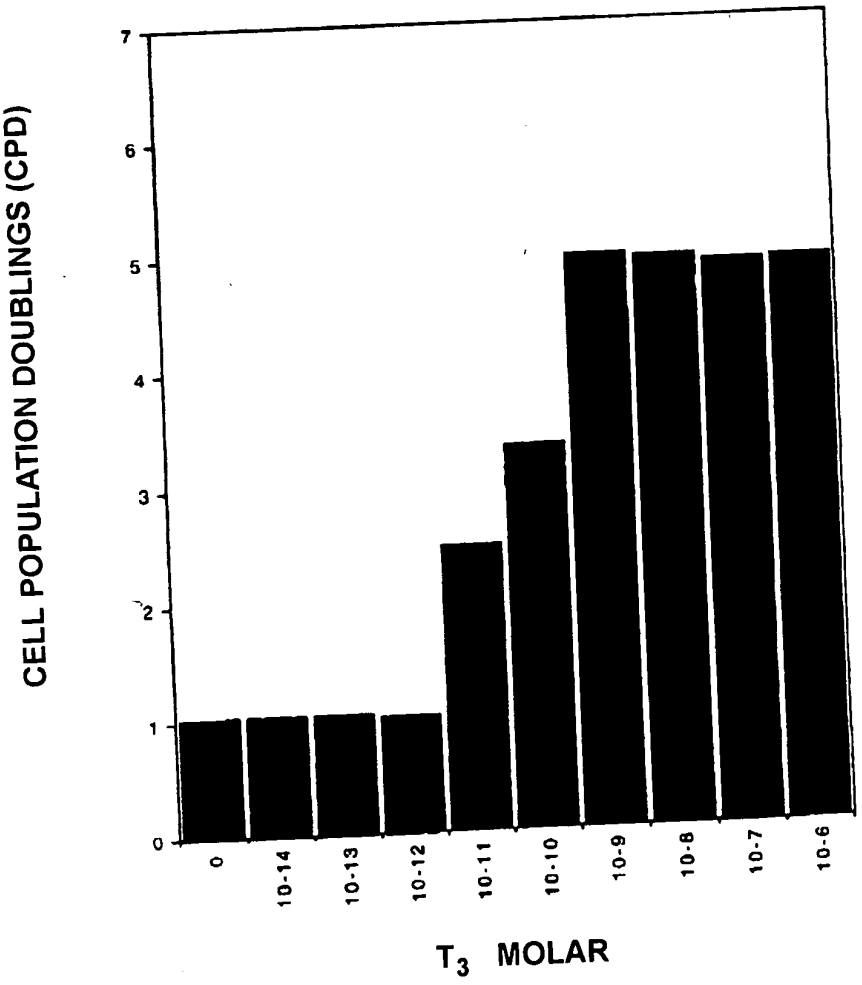


FIGURE 15

E_2 TITRATION OF GH_3 CELLS GROWN IN SERUM-FREE MEDIUM MINUS T_3

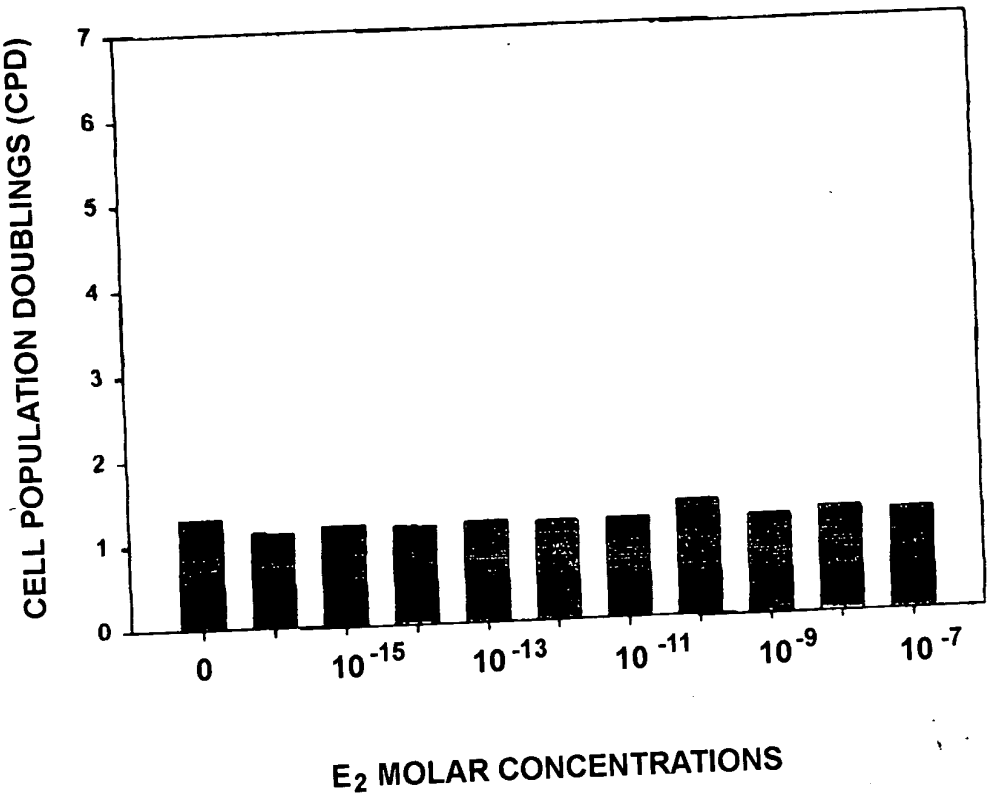


FIGURE 16

EFFECT OF T_3 ON GH CELL LINES: GROWTH IN 2.5% CDE - HORSE SERUM WITH NO E_2

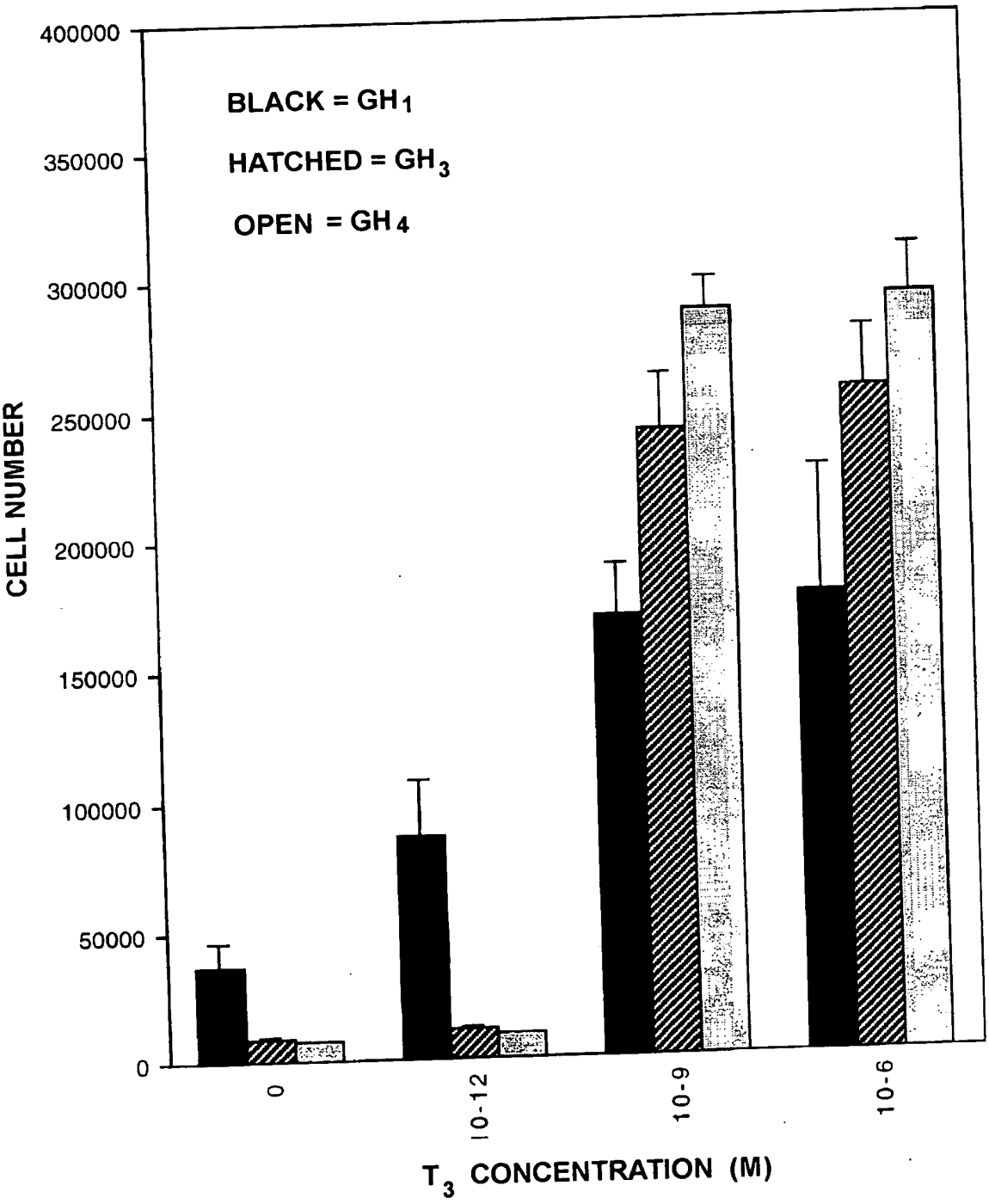


FIGURE 17

EFFECT OF T_3 ON PITUITARY CELL LINES INCUBATED IN 50% CDE - HORSE SERUM

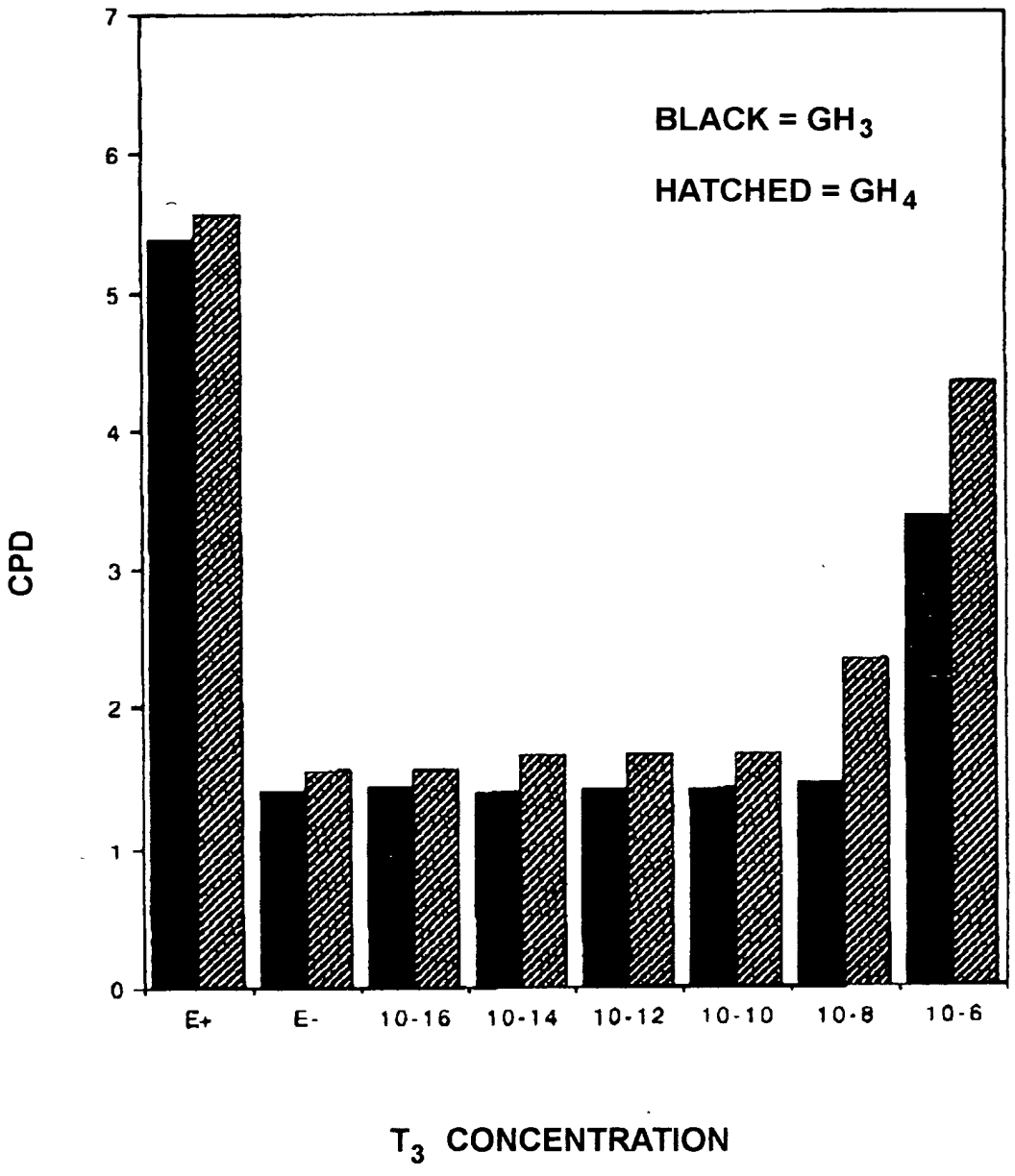
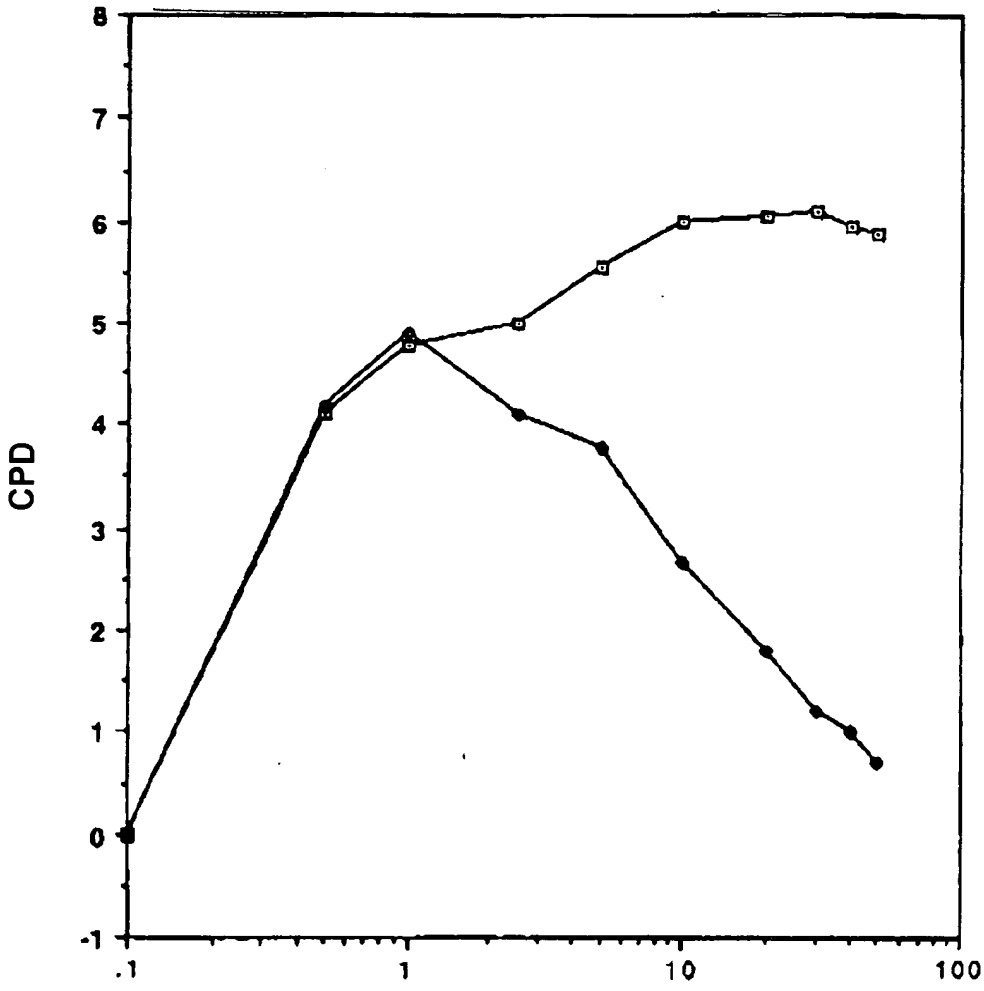


FIGURE 18

EFFECT OF XAD-4 RESIN TREATED HORSE SERUM ON MTW9/PL2 CELL GROWTH $\pm E_2$



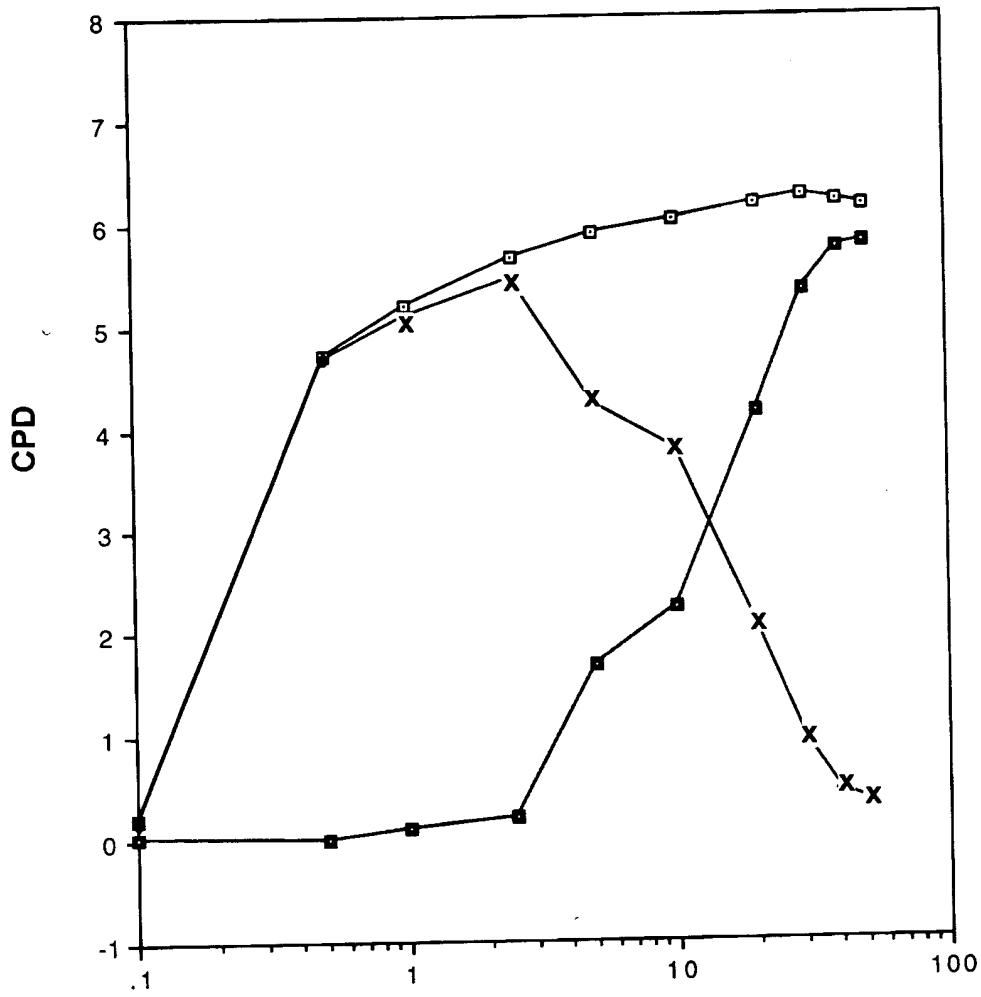
LEGEND:

Open squar s = + E_2

Closed squares = - E_2

FIGURE 19

EFFECT OF XAD-4 RESIN TREATED HORSE SERUM ON T47D CELL GROWTH $\pm E_2$



LEGEND:

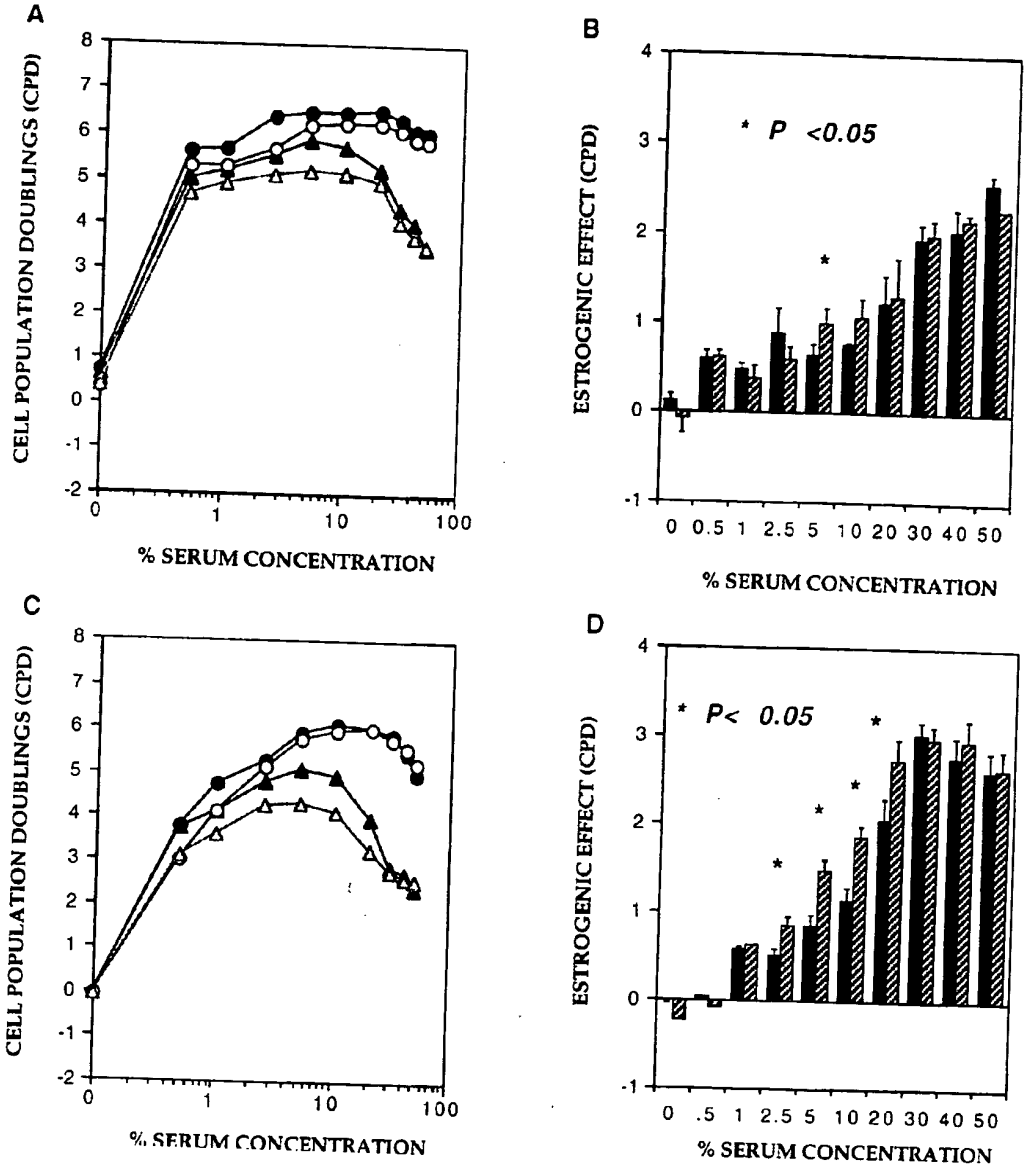
Open squares = + E_2

XXX = - E_2

Closed squares = Estrogenic effect

FIGURE 20

MCF-7 CELL GROWTH IN CDE - HORSE SERUM ± PHENOL RED AND ± E_2

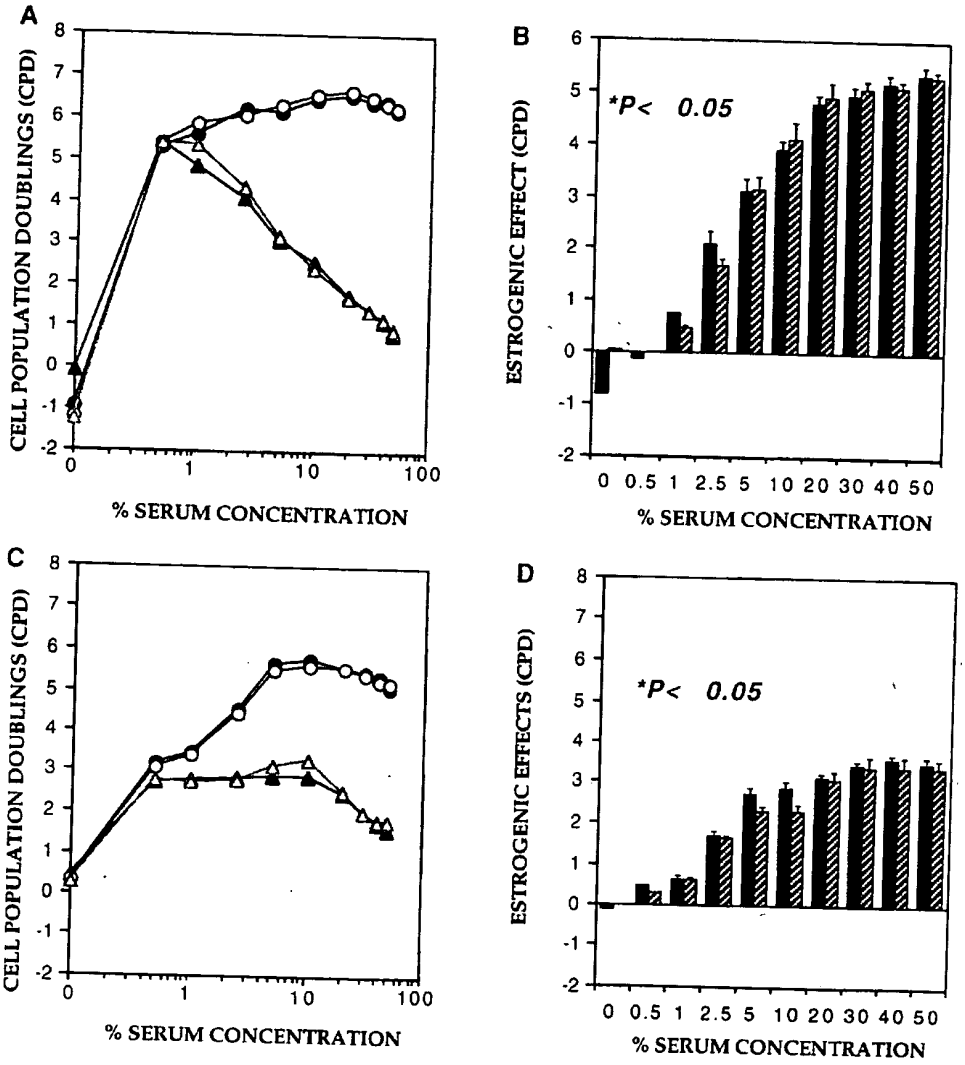


LEGEND:

(A) MCF-7A cell growth in phenol red containing medium with E_2 (closed circles) and without E_2 (closed triangles), and in phenol red-free medium with E_2 (open circles) and without E_2 (open triangles).
(B) Estrogenic effects with MCF-7A cells in medium with phenol red (solid bars) and without phenol red (shaded bars) were calculated from (A) and defined as the CPD in medium containing E_2 minus the CPD in medium without added E_2.
(C) MCF-7K cell growth in phenol red medium with E_2 (closed circles) and without E_2 (closed triangles), and in phenol red-free medium with E_2 (open circles) and without E_2 (open triangles).
(D) Estrogenic effects with MCF-7K cells in medium with phenol red (solid bars) and without phenol red (shaded bars), calculated from (C).

FIGURE 21

T47D AND ZR-75-1 CELL GROWTH IN CDE-HS ± PHENOL RED AND ± E_2

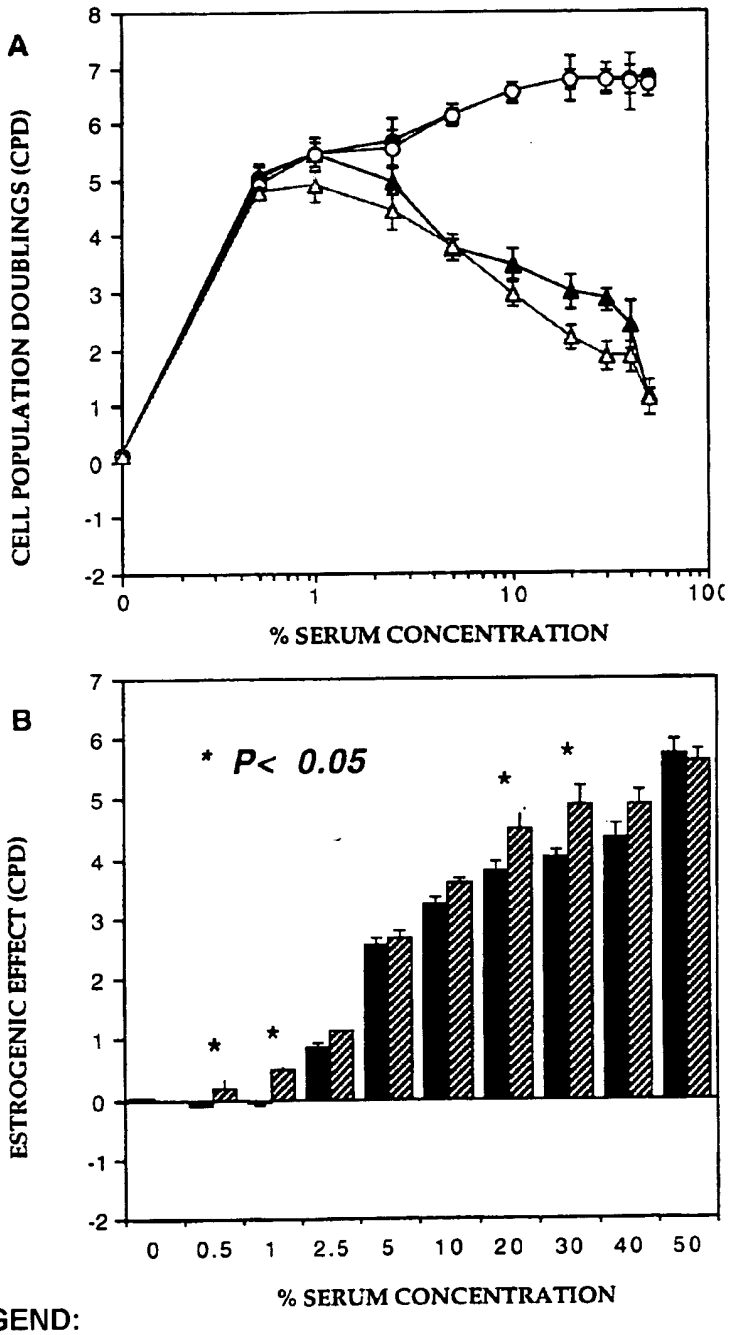


LEGEND:

(A) T47D cell growth in phenol red containing medium with E_2 (closed circles) and without E_2 (closed triangles), and in phenol red-free medium with E_2 (open circles) and without E_2 (open triangles).
(B) Estrogenic effects with T47D cells in medium with phenol red (solid bars) and without phenol red (shaded bars) were calculated from (A) and defined as the CPD in medium containing E_2 minus the CPD in medium without added E_2.
(C) ZR-75-1 cell growth in phenol red medium with E_2 (closed circles) and without E_2 (closed triangles), and in phenol red-free medium with E_2 (open circles) and without E_2 (open triangles).
(D) Estrogenic effects with ZR-75-1 cells in medium with phenol red (solid bars) and without phenol red (shaded bars), calculated from (C).

FIGURE 22

MTW9/PL2 CELL GROWTH IN CDE - HORSE SERUM ± PHENOL RED AND ± E_2



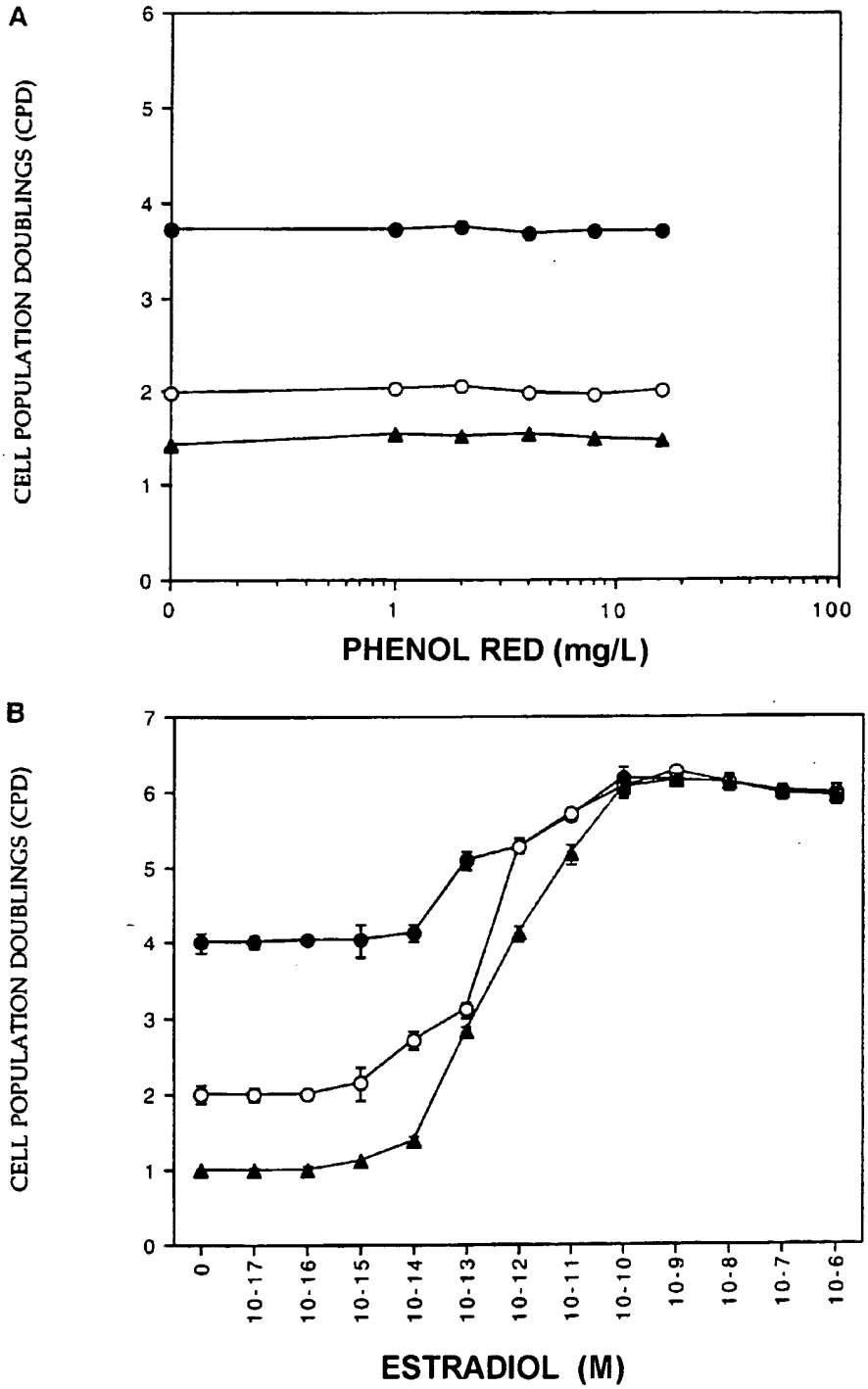
LEGEND:

(A) MTW9/PL2 growth in phenol red medium with E_2 (closed circles) and without E_2 (closed triangles), and in phenol red-free medium with E_2 (open circles) and without E_2 (open triangles).

(B) Estrogenic effects with MTW9/PL2 cells in medium with phenol red (solid bars) and without (shaded bars) were calculated from (A).

FIGURE 23

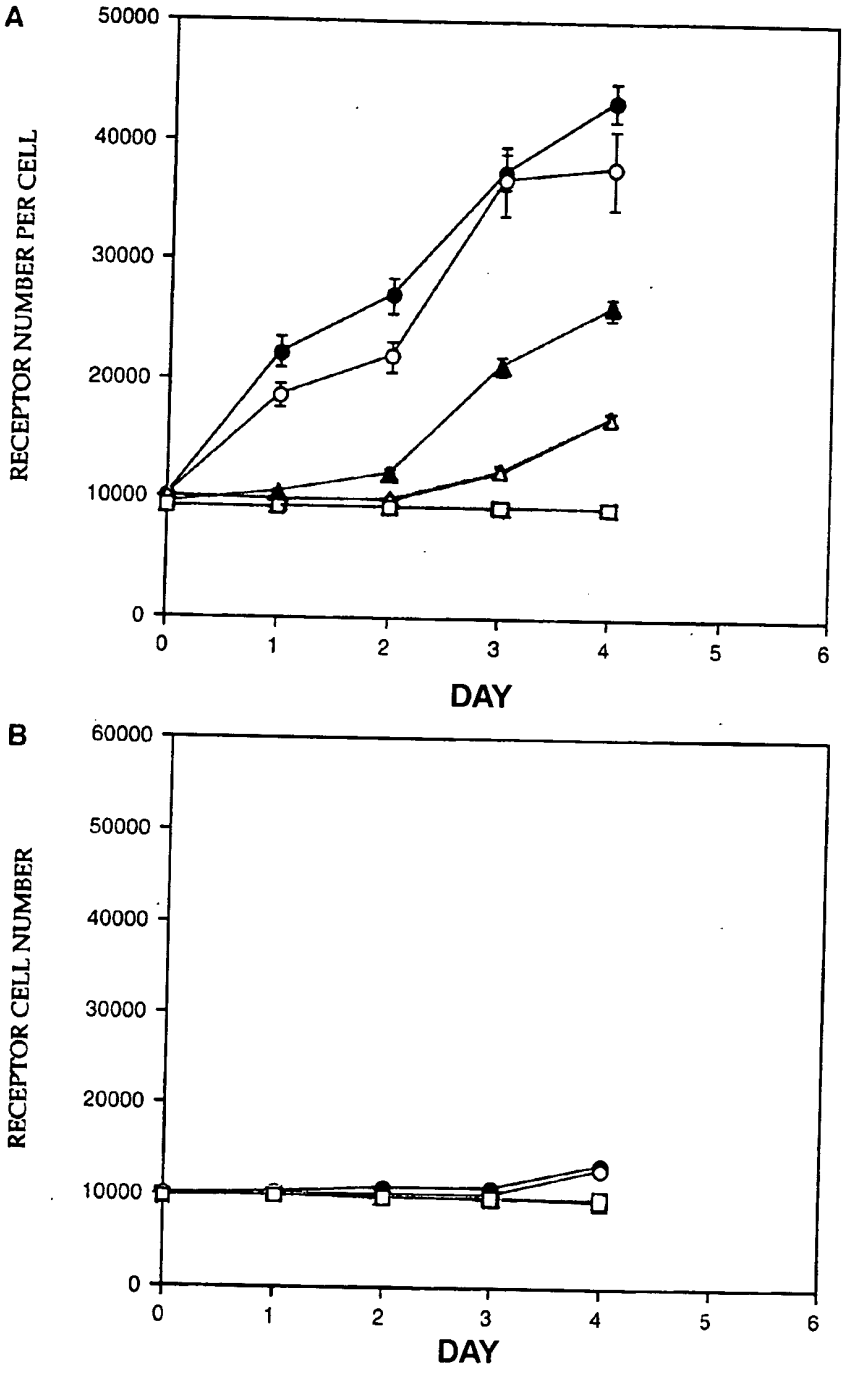
DOSE RESPONSE TO PHENOL RED AND E_2 IN THREE CELL LINES



LEGEND: The growth of the MCF-7A (closed circles), MTW9/PL2 (open circles) and T47D (closed triangles) cell lines was assessed at 14, 7, and 12 days.

FIGURE 24

PROGESTERONE RECEPTOR INDUCTION IN T47D CELLS BY PHENOL RED AND E_2



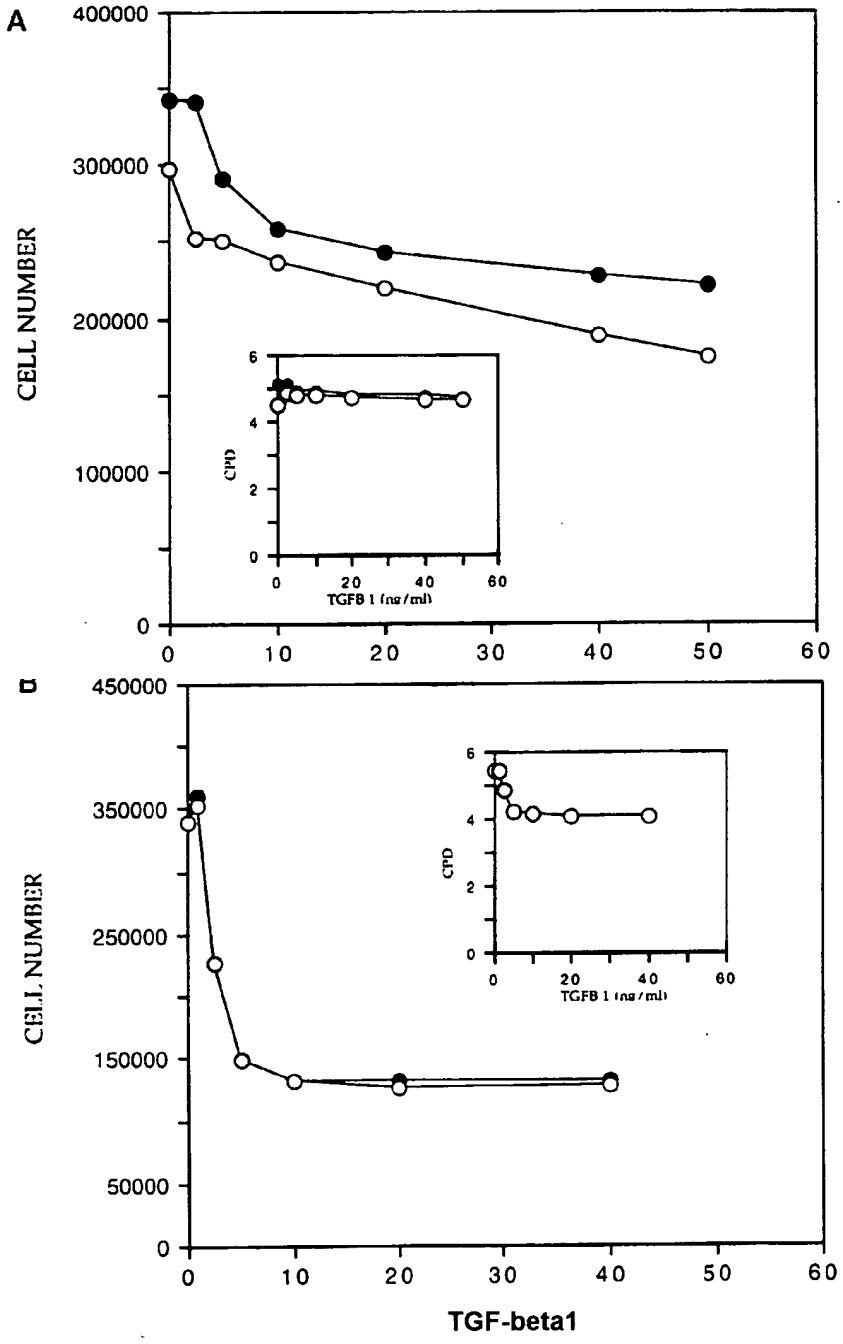
LEGEND:

(A) The effects of E_2 at 1.0×10^{-8} M (closed circles), 1.0×10^{-10} M (open circles), 1.0×10^{-12}M (closed triangles), 1.0×10^{-14} M (open triangles) and the control without added E_2 (open squares).

(B) The effects of phenol red at 16 mg/L (closed circles), 8mg/L (open circles), 4 mg/L (closed triangles), 2 mg/L (open triangles), and the control without phenol red (open squares).

FIGURE 25

EFFECT OF TGF-beta1 ON THE GROWTH OF BREAST/MAMMARY ORIGIN CELL LINES



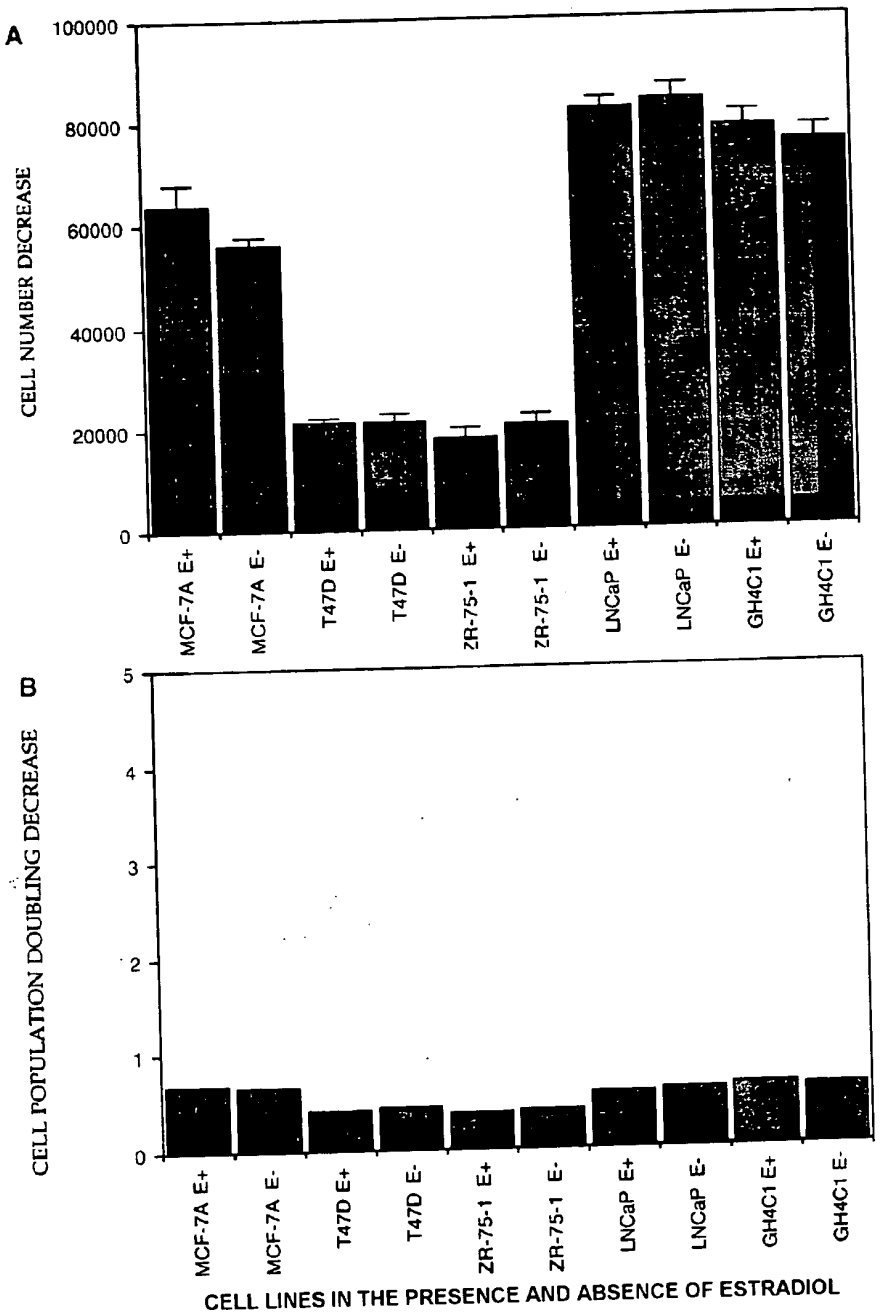
LEGEND:

(A) The effect of the transforming growth inhibitor on human breast MCF-7K cell growth as measured after 12 d either with 10 nM E_2 (closed circles) or without the hormone (open circles). The insert shows conversion of the cell number results to CPD.

(B) The same experiment with rat mammary MTW9/PL2 cells after 9 d growth.

FIGURE 26

EFFECT OF TGF-beta1 ON THE GROWTH OF CELL LINES FROM BOTH HUMAN AND RODENT TUMORS

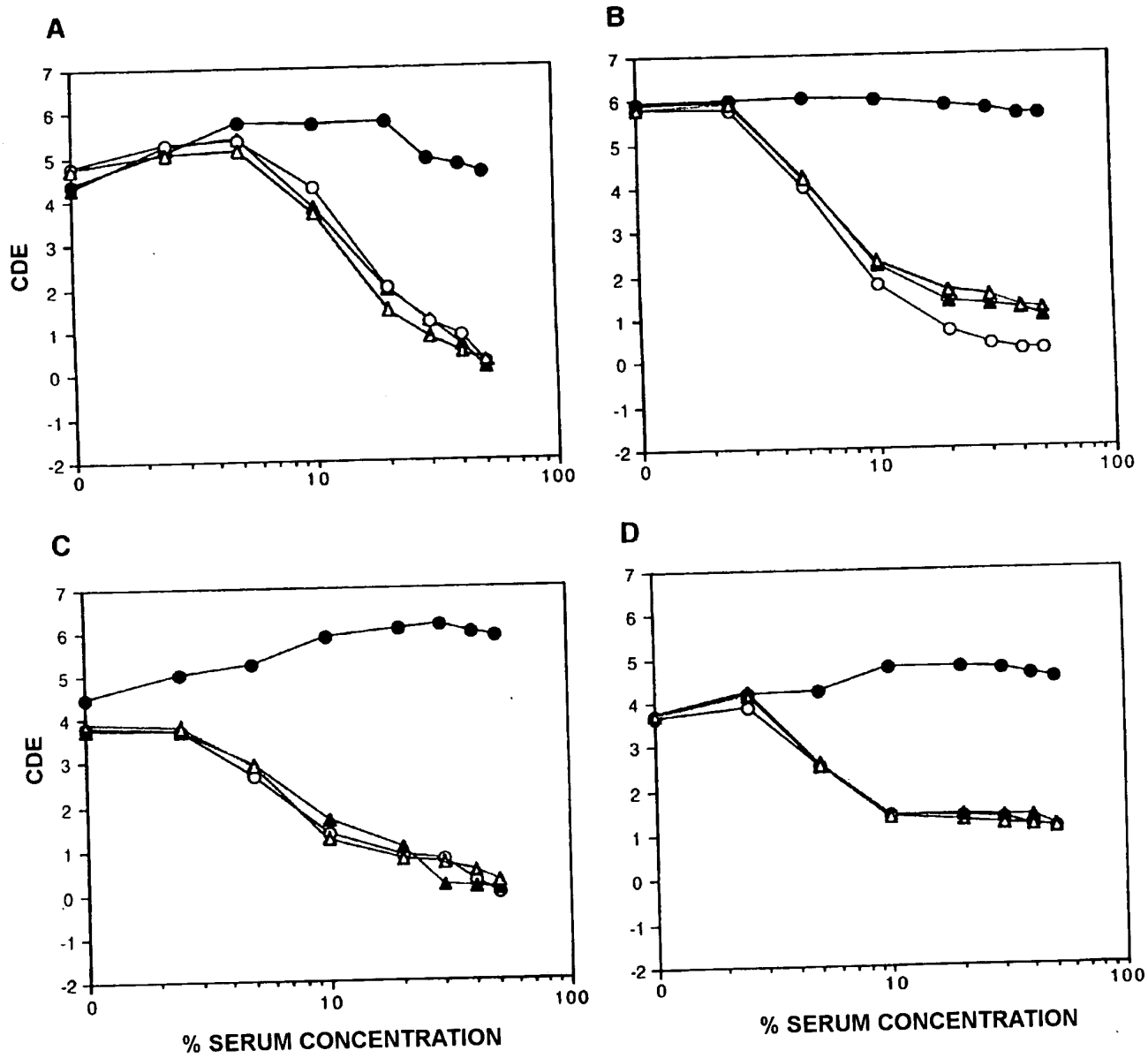


In these studies, TGF-beta1 was added at 40 ng/ml. Estradiol (± E) indicates either no added E_2 or the steroid at 10 nM.

(A) The effect of TGF-beta1 on five cell lines after 10-14 d growth in medium ± E_2. Th results are expressed as cell number decreases caused by TGF-beta1.
(B) The CPD d creases caused by TGF-beta1 ± E_2 with each of the cell lines shown in (A).

FIGURE 27

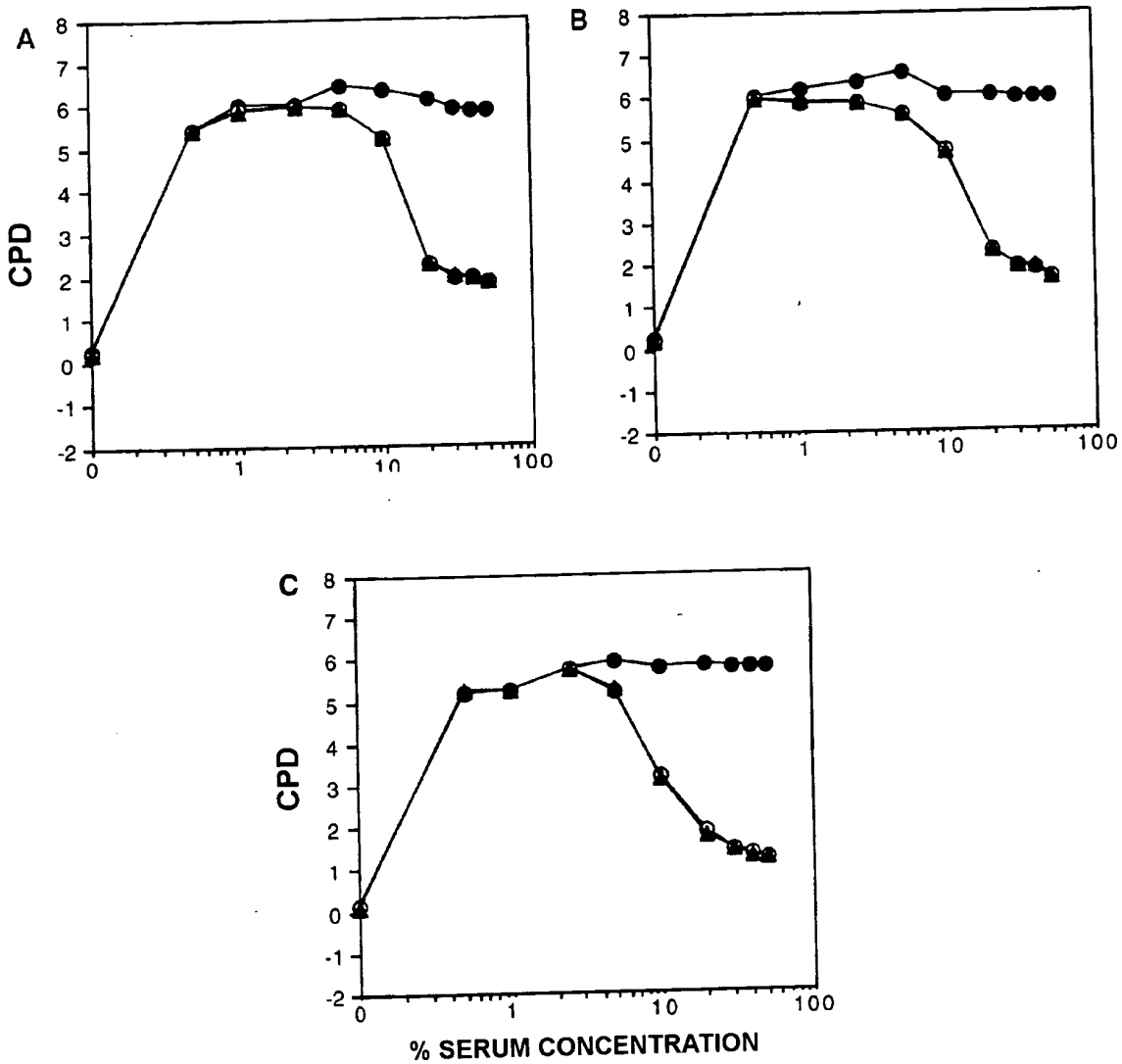
EFFECT OF EGF AND TGF-alpha ON THE GROWTH OF HUMAN BREAST CANCER CELLS



The cells were grown in D-MEM/F-12 supplemented with increasing concentrations of CDE horse serum. Each line tested was grown in serum alone (open circles) and in serum plus 50 ng/ml EGF (open triangles), 50 ng/ml TGF-alpha (closed triangles), or 10 nM E_2 without exogenous growth factors (closed circles). (A) - (D) show the results with the MCF-7A, MCF-7K, T47D, and ZR-75-1 cell lines, respectively.

FIGURE 28

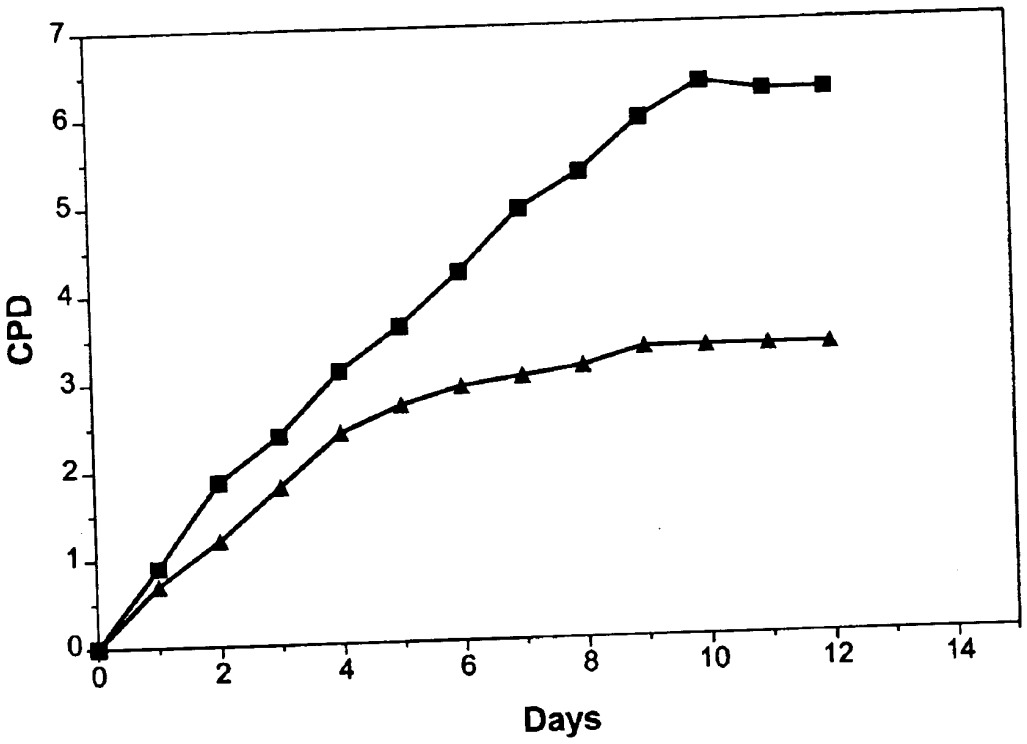
EFFECT OF IGF-I ON THE GROWTH OF HUMAN BREAST CANCER CELLS



Breast cancer cells were grown in D-MEM/F-12 supplemented with increasing concentrations of CDE horse serum. Each cell line tested was grown in serum alone (open circles) and in serum plus 1.0 ug/ml IGF-I (triangles), or in serum with 10 nM E_2 without exogenous growth factors (closed circles). (A) - (C) show the results with the MCF-7K, MCF-7A and T47D cells, respectively. Assays were conducted for 12-14 d.

FIGURE 29

T47D CELLS IN STANDARD D-MEM/F-12 MEDIUM VS "LOW FE" SERUM-FREE SERUM



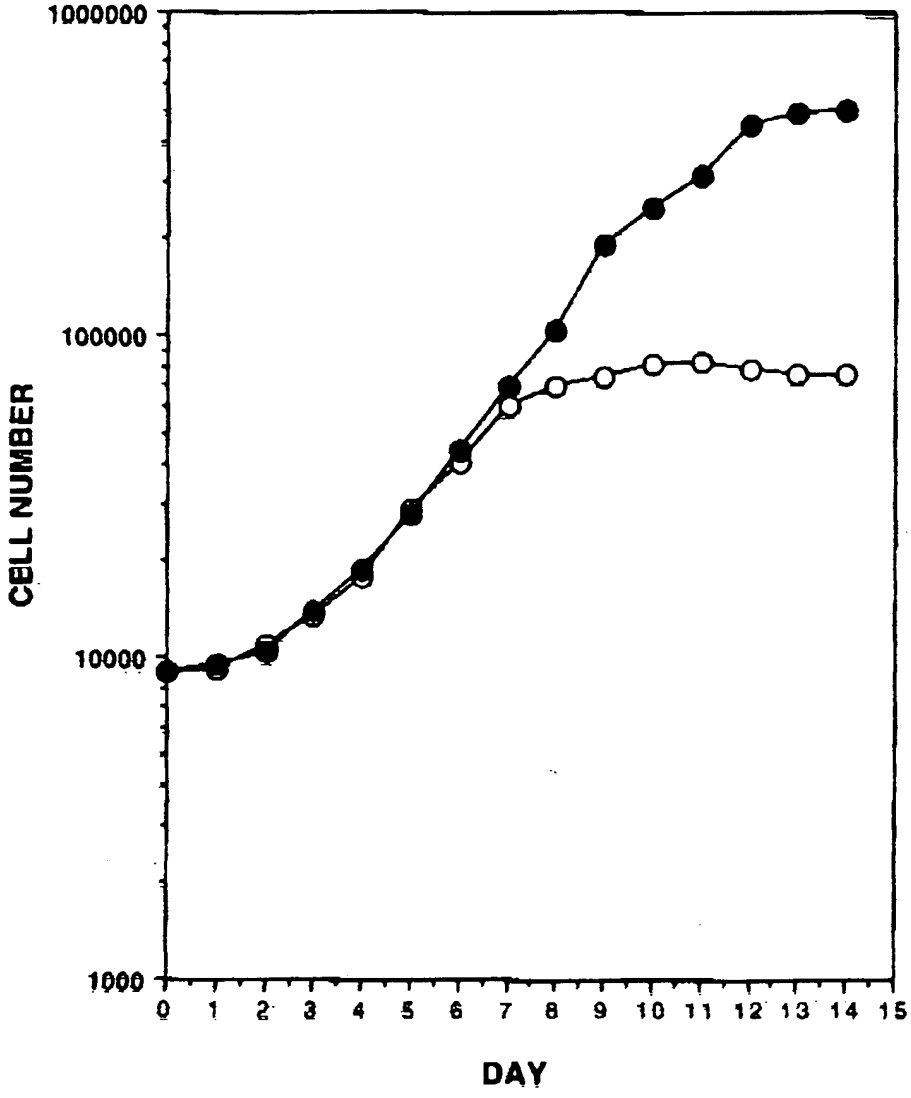
LEGEND:

"STANDARD" MEDIUM

"LOW-FE" MEDIUM

FIGURE 30

LNCaP CELLS IN STANDARD D-MEM/F-12 MEDIUM VS "LOW-FE" SERUM-FREE MEDIUM



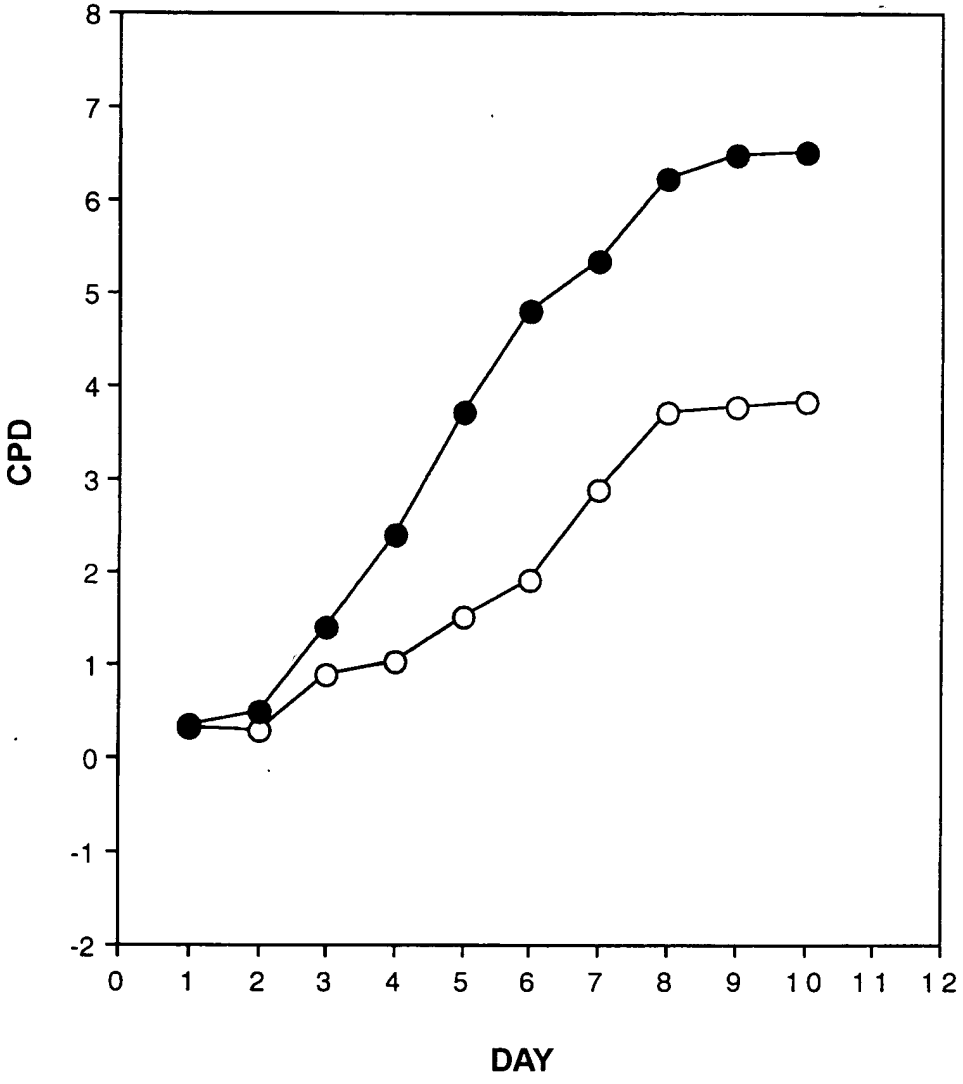
LEGEND:

"STANDARD" MEDIUM

"LOW-FE" MEDIUM

FIGURE 31

MDCK CELLS IN STANDARD D-MEM/F-12 MEDIUM VS "LOW FE" SERUM-FREE MEDIUM



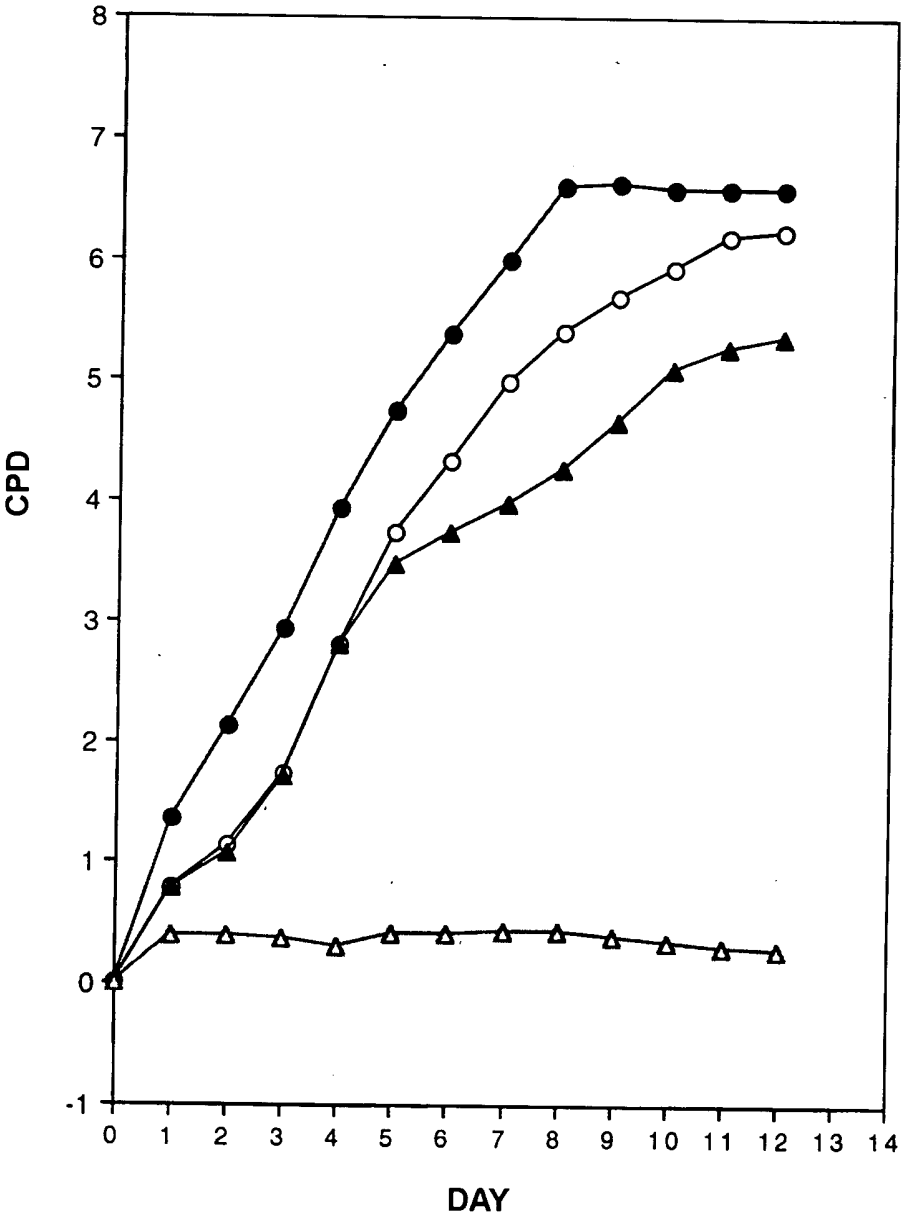
LEGEND:

—○— "STANDARD" MEDIUM

—●— "LOW-FE" MEDIUM

FIGURE 32

LNCaP CELL GROWTH IN CAPM ± DHT AND 10% FETAL BOVINE SERUM

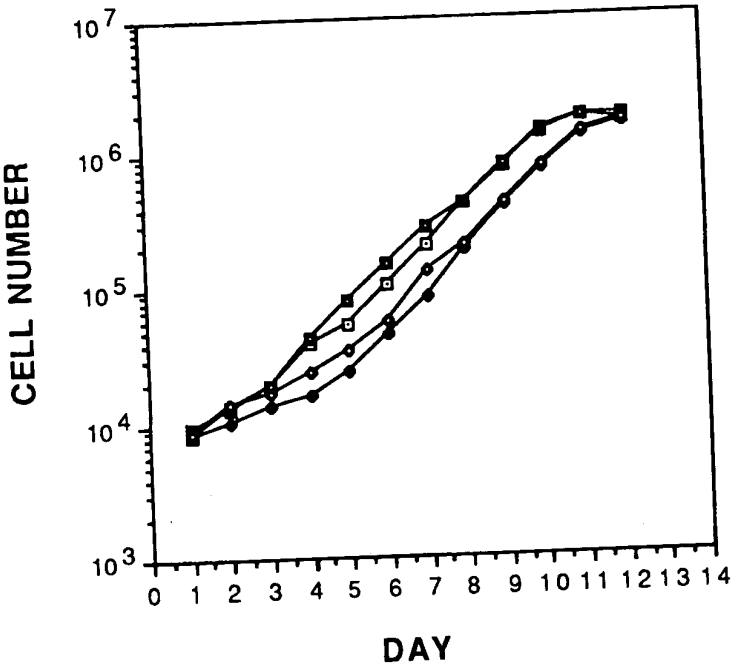


LEGEND:

Closed circles = Fetal bovine serum
Open circles = CAPM + DHT
Closed triangles = CAPM - DHT
Open triangles = D-MEM/F12 only

FIGURE 33

PC3 AND DU145 GROWTH IN SERUM - FREE MEDIUM VS MEDIUM WITH 10% FETAL CALF SERUM



LEGEND:

PC3 IN SERUM-FREE MEDIUM

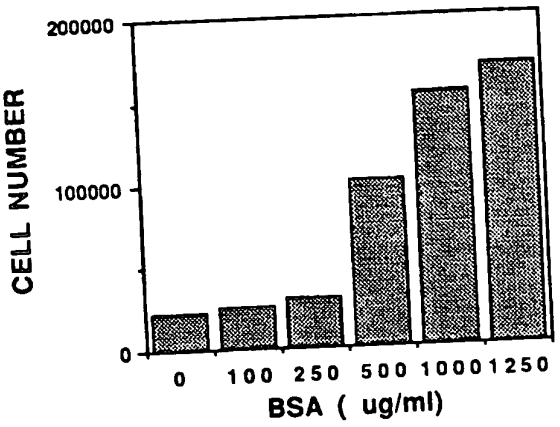
DU145 IN SERUM-FREE MEDIUM

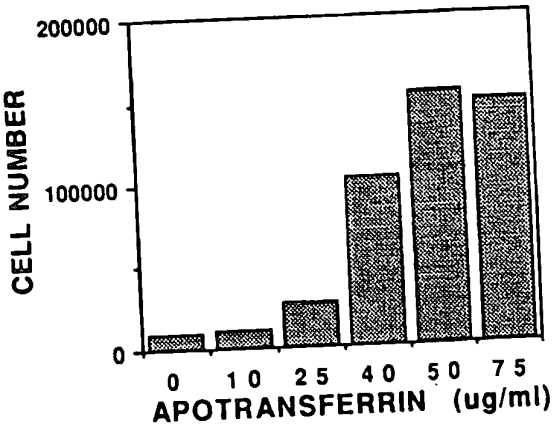
PC3 IN 10% FETAL CALF SERUM

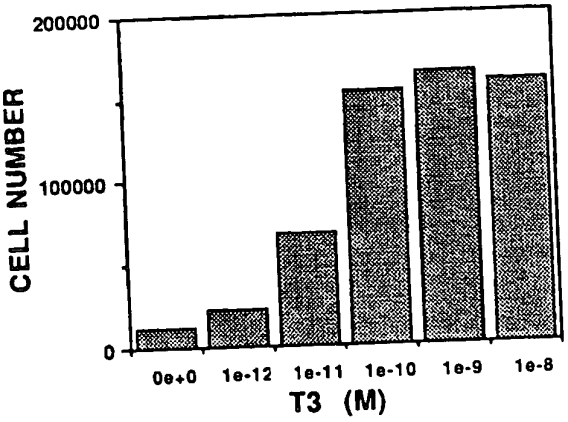
DU145 IN 10% FETAL CALF SERUM

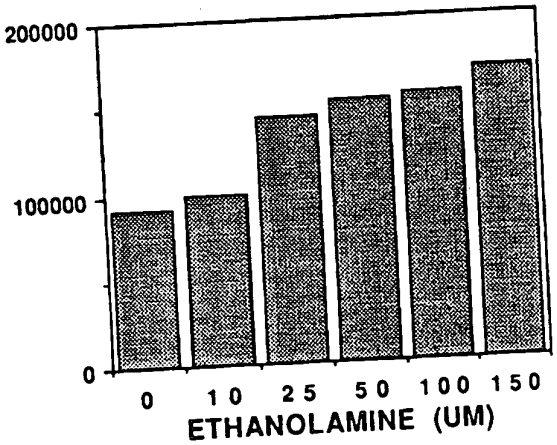
FIGURE 34

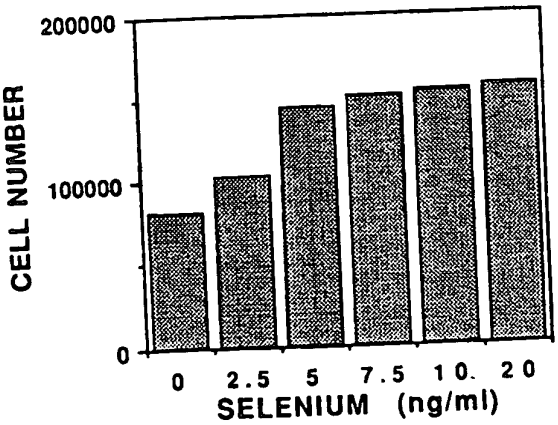
DOSE-RESPONSE EFFECTS OF INDIVIDUAL COMPONENTS OF CAPM SERUM-FREE MEDIUM ON LNCAP CELL GROWTH











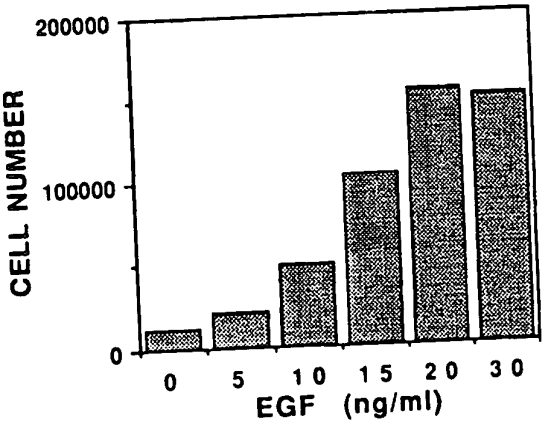
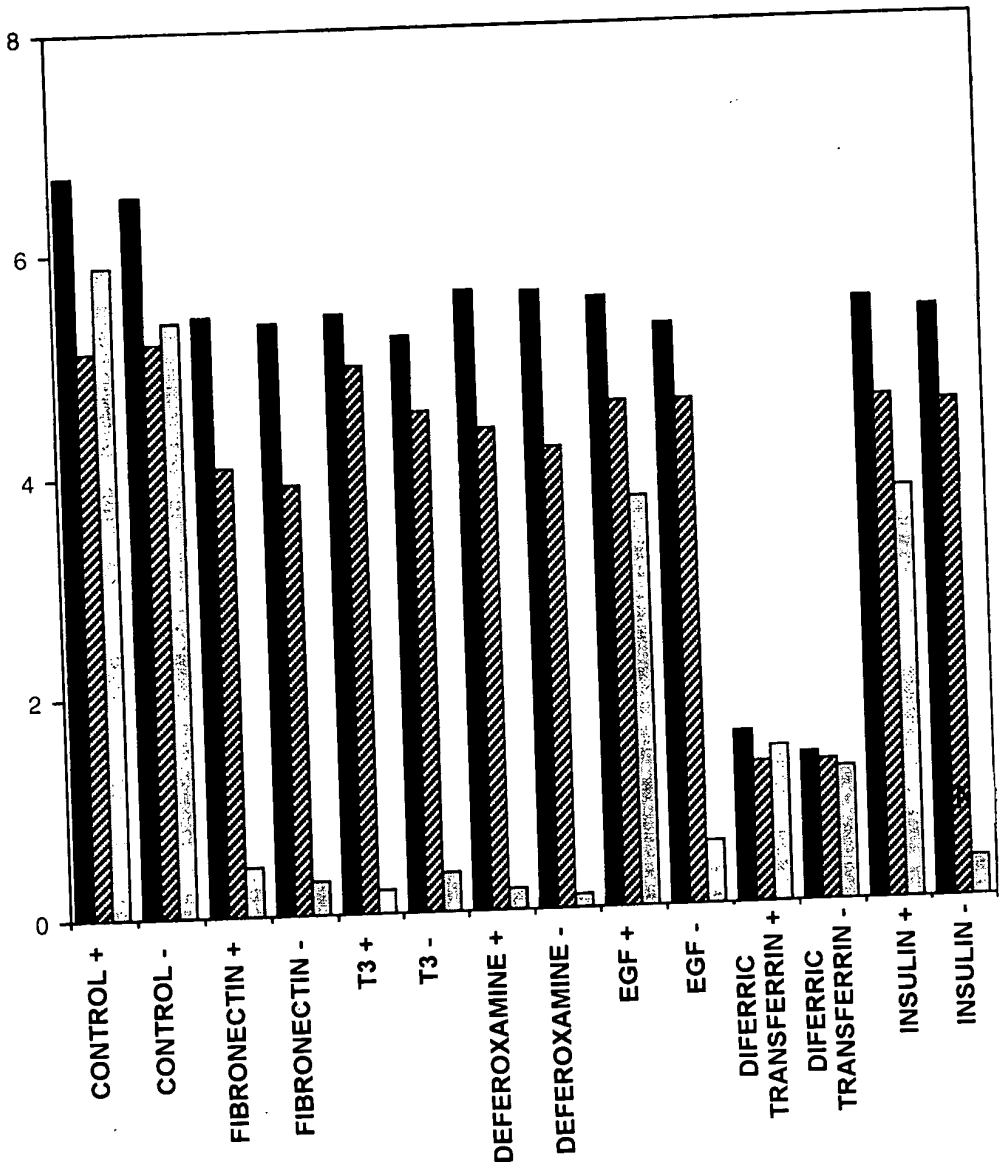


FIGURE 35

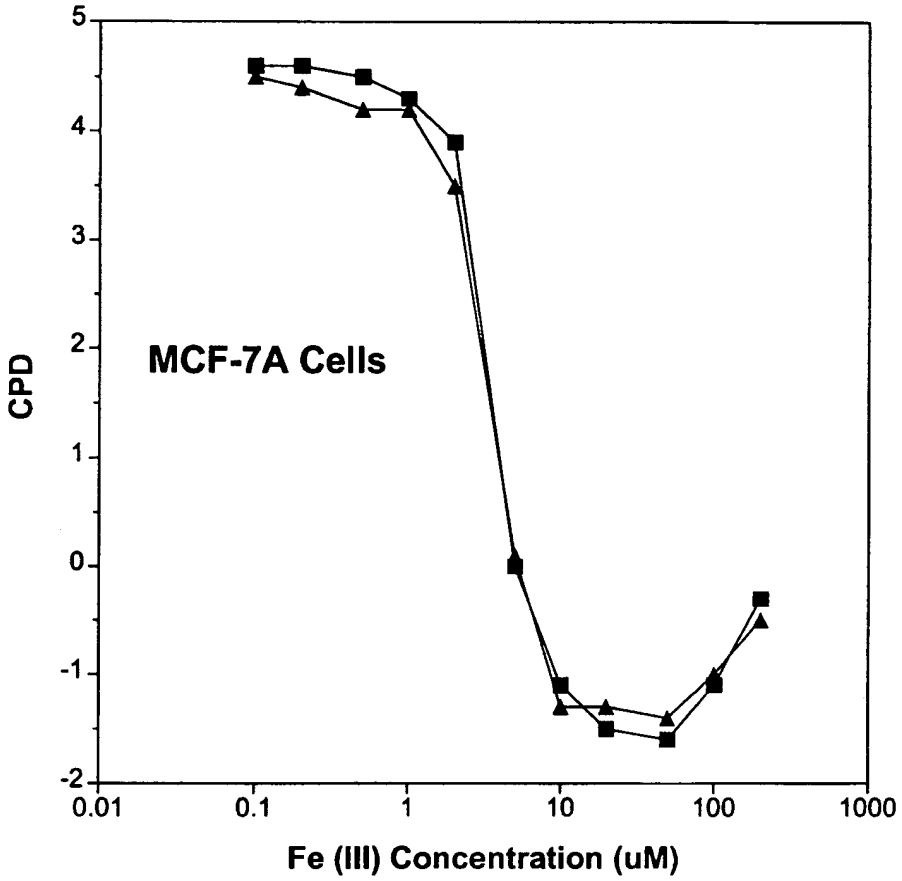
DELETIONS OF INDIVIDUAL COMPONENTS OF CAPM WITH PROSTATE CANCER CELL LINES



LEGEND:
■ = PC3
▨ = DU145
□ = LNCaP
\+ = 10 nM DHT
− = NO DHT

FIGURE 36

EFFECT OF FE (III) IN MCF-7A CELL GROWTH IN DDM-2MF DEFINED MEDIUM



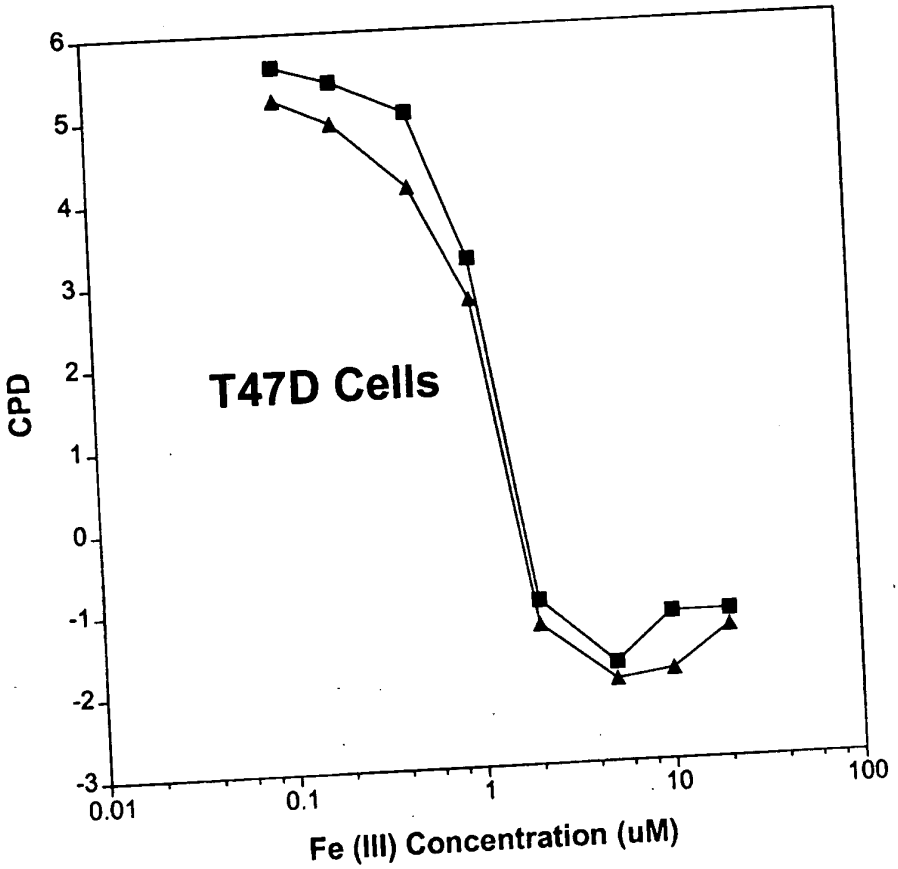
LEGEND:

plus E_2

minus E_2

FIGURE 37

EFFECT OF FE (III) IN T47D CELL GROWTH IN DDM-2MF DEFINED MEDIUM



LEGEND:

plus E_2

minus E_2

FIGURE 38

EFFECTS OF INCREASING CONCENTRATIONS OF IRON ON LNCaP CELLS GROWN IN SERUM-FREE MEDIUM WITH APOTRANSFERRIN

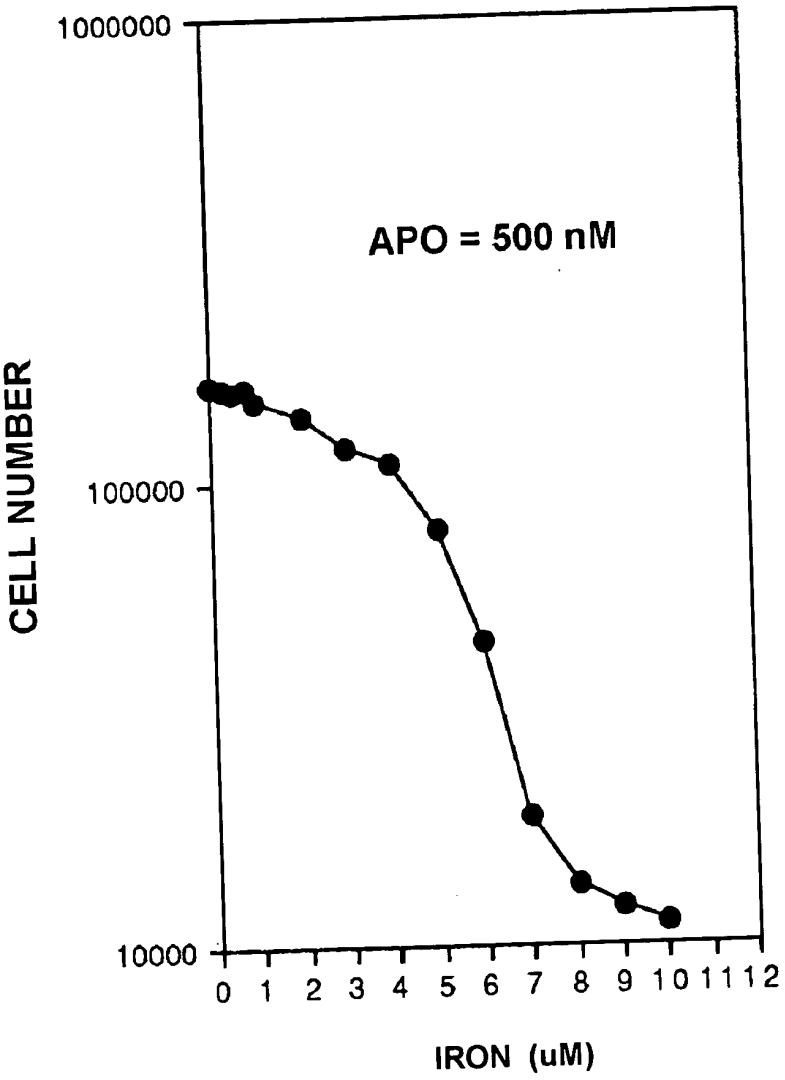
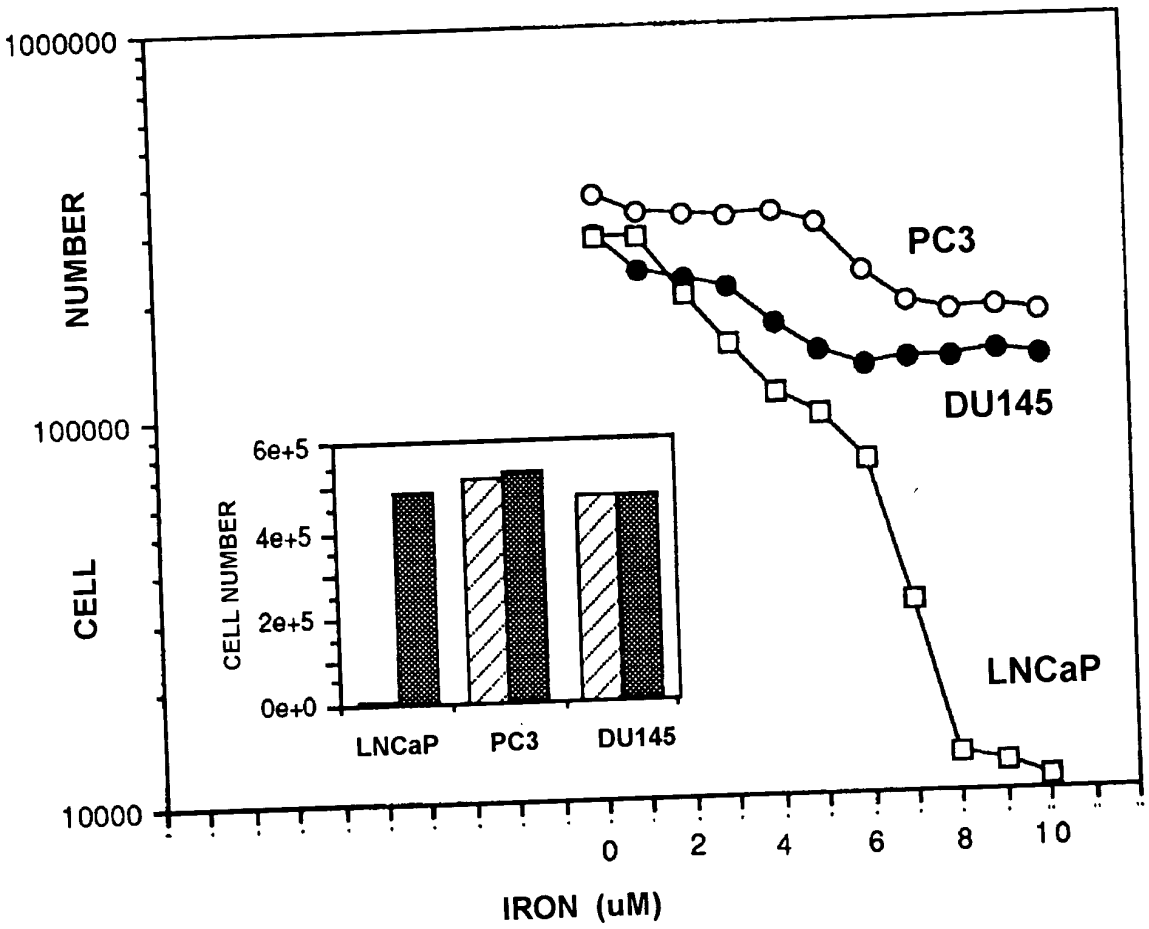


FIGURE 39

EFFECTS OF IRON AND T_3 ON THREE PROSTATIC CELL LINES IN SERUM-FREE MEDIUM



INSERT:

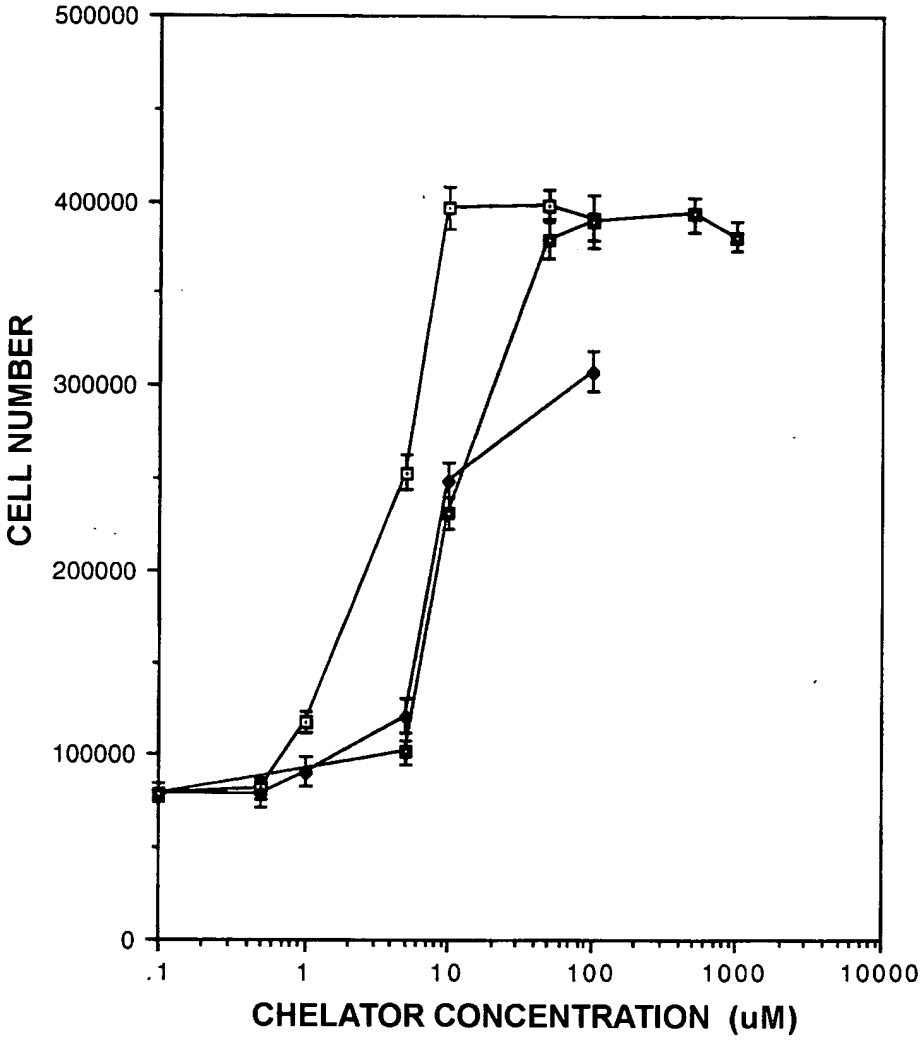
DARK BARS = GROWTH IN CAPM PLUS T_3

LIGHT (HATCHED) BARS = GROWTH IN CAPM MINUS T_3

NOTE THE STRIKING DEPENDENCE OF LNCaP CELLS ON T_3

FIGURE 40

EFFECT OF CHELATORS ON SERUM-FREE T47D GROWTH UNDER HIGH IRON CONDITIONS



LEGEND:

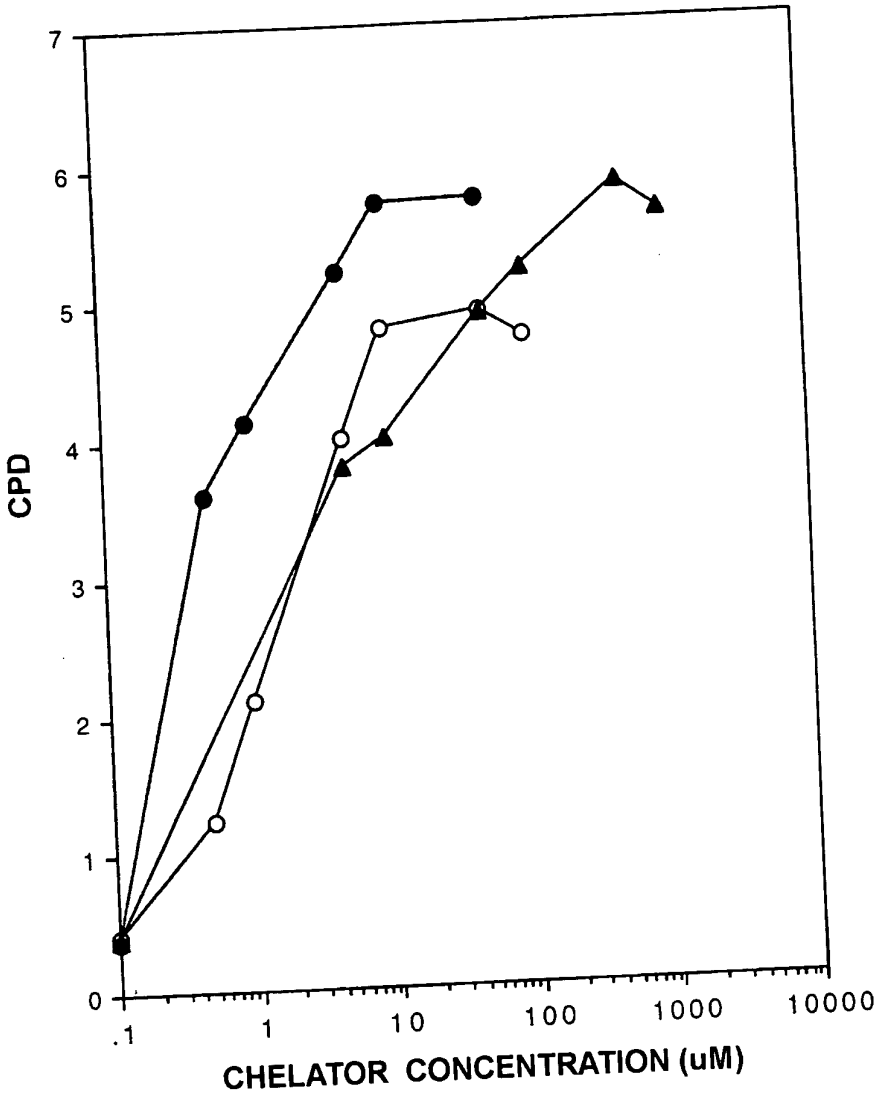
DEFEROXAMINE

EDTA

CITRATE

FIGURE 41

EFFECT OF CHELATORS ON SERUM-FREE LNCaP GROWTH UNDER HIGH IRON CONDITIONS



LEGEND:

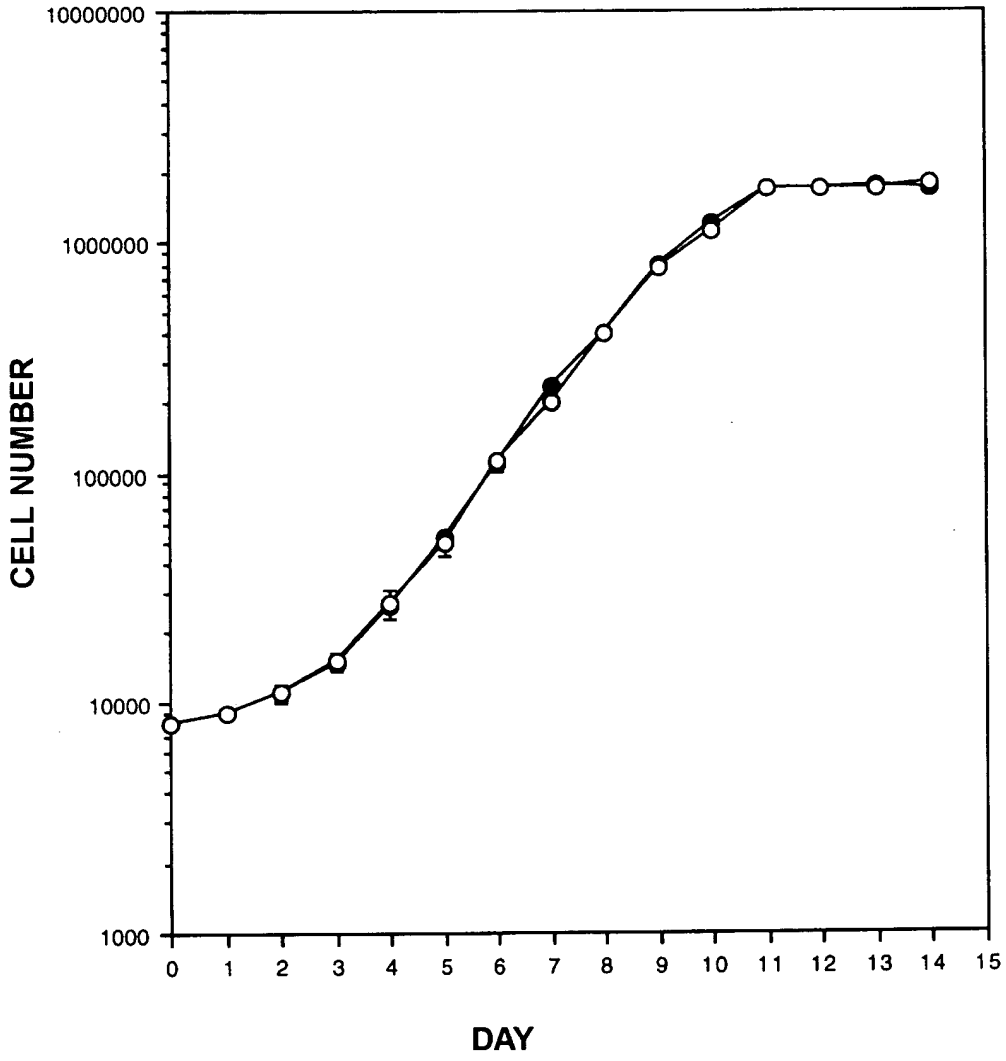
Closed circles = Deferoxamine

Open circles = Citrate

Closed triangles = EDTA

FIGURE 42

DU145 GROWTH IN SERUM-FREE MEDIUM BASED ON "LOW FE" OR "STANDARD" MEDIUM



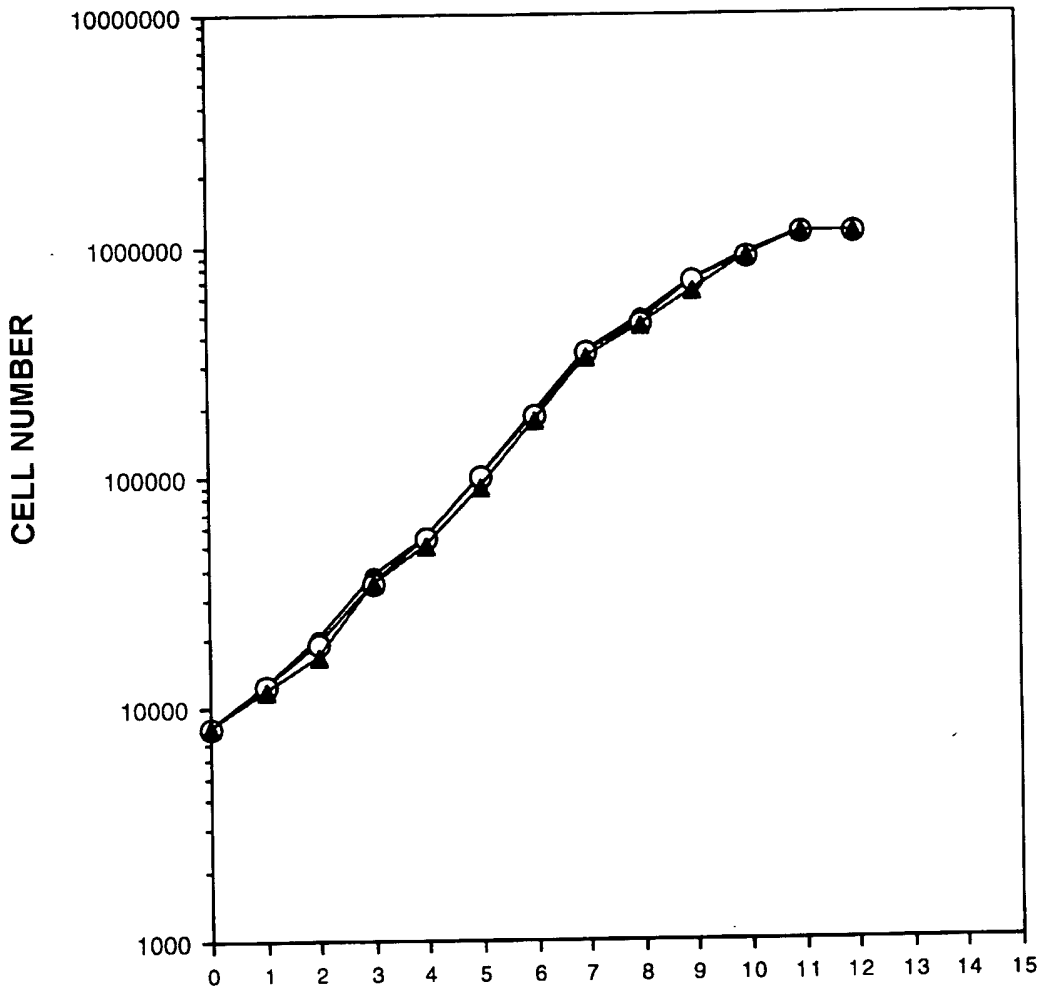
LEGEND:

Open circles = "Low Fe" medium

Closed circles = "Standard" medium

FIGURE 43

PC3 GROWTH IN SERUM-FREE MEDIUM BASED ON "LOW FE" OR "STANDARD" MEDIUM



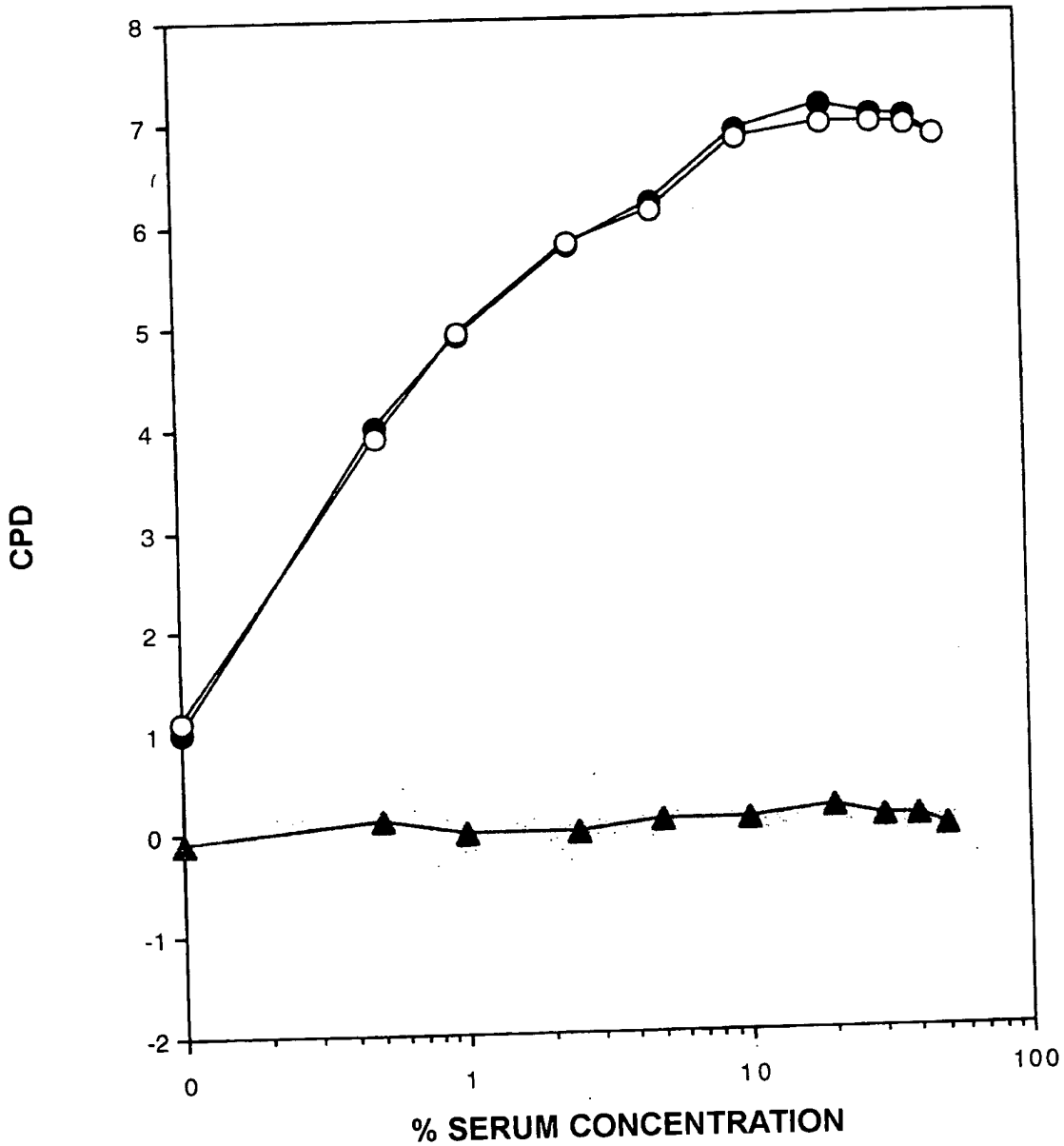
LEGEND:

Open circles = "Low Fe" medium

Closed triangles = "Standard" medium

FIGURE 44

CDE HORSE SERUM TITRATION ON DU145 CELLS



LEGEND:

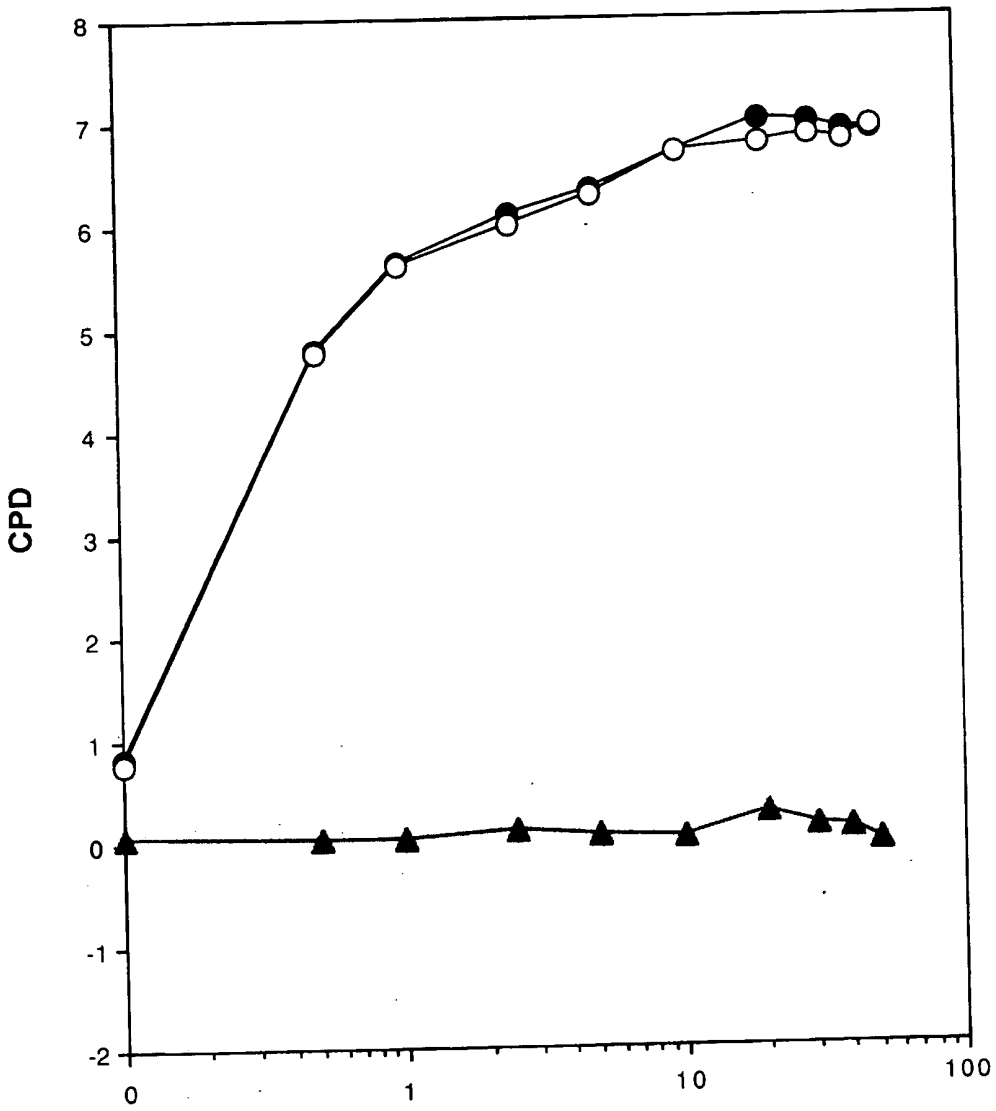
—●— = + 10 nM DHT

—○— = STEROID FREE

—▲— = ANDROGENIC EFFECT

FIGURE 45

CDE HORSE SERUM TITRATION ON PC3 CELLS



LEGEND:

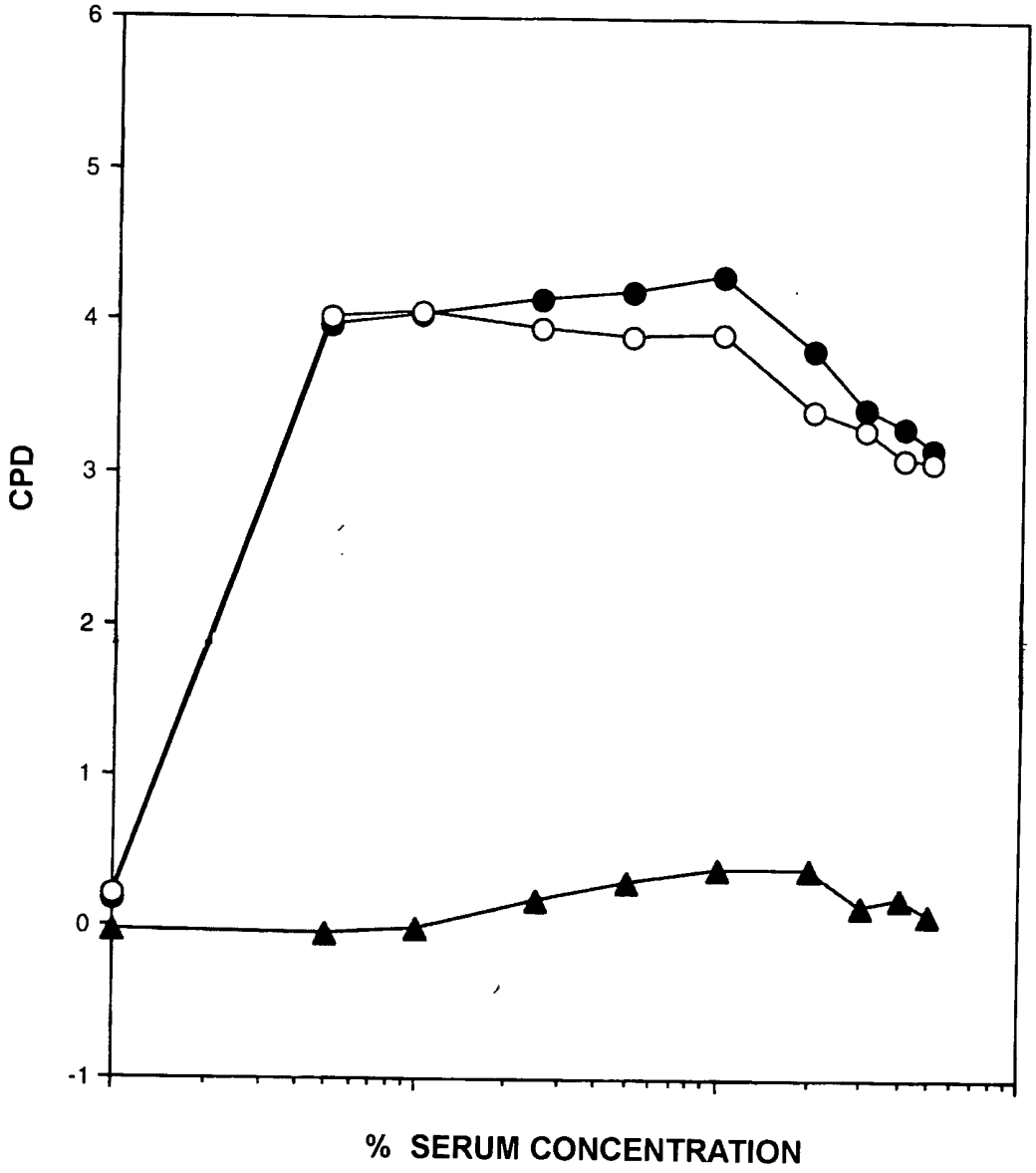
= + 10 nM DHT

= STEROID FREE

= ANDROGENIC EFFECT

FIGURE 46

CDE HORSE SERUM TITRATION ON ALVA-41 CELLS



LEGEND:

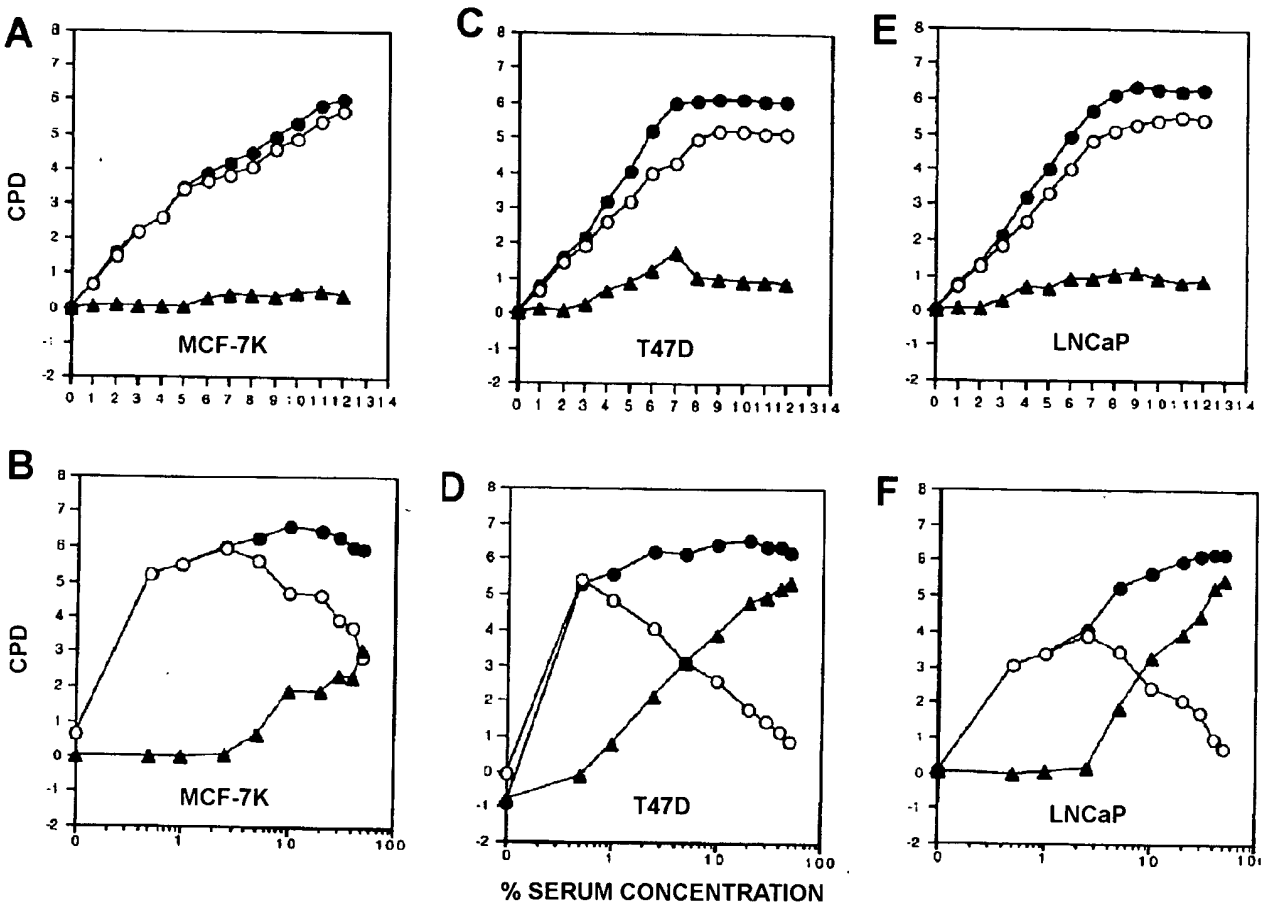
● = + 10 nM DHT

○ = STEROID FREE

▲ = ANDROGENIC EFFECT

FIGURE 47

EFFECTS OF ESTROGEN ON STEROID HORMONE-RESPONSIVE HUMAN TUMOR CELL GROWTH

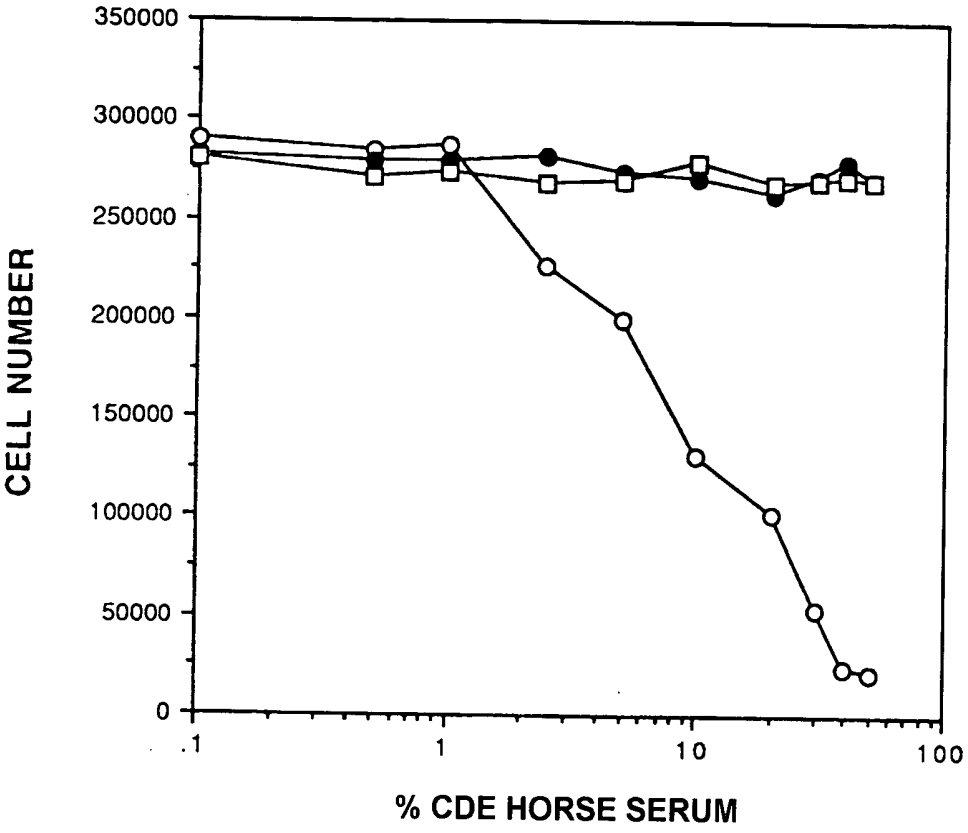


The cells were grown in serum-free defined medium and in D-MEM/F-12 supplemented with increasing concentrations of CDE horse serum.

(A) MCF-7K cell growth was measured daily in serum-free defined DDM-2MF with 10 nM E_2 (closed circles) and without steroid (open circles) E_2 . Triangles = estrogenic effect.
(B) MCF-7K cell growth measured after 12 d in D-MEM-F-12 supplemented with the designated concentrations of serum with E_2 (closed circles) and without steroid (open circles). The estrogenic effect is shown by triangles.
(C) and (D) show the same experiments as in (A) and (B), respectively, except with T47D cells.
(E) and (F) show the same experiments as in (A) and (B), respectively, xcept with LNCaP cells. In (E) the serum-free medium was CAPM.

FIGURE 48

CDE HORSE SERUM TITRATION ON LNCaP GROWTH IN SERUM FREE CONDITIONS



LEGEND:

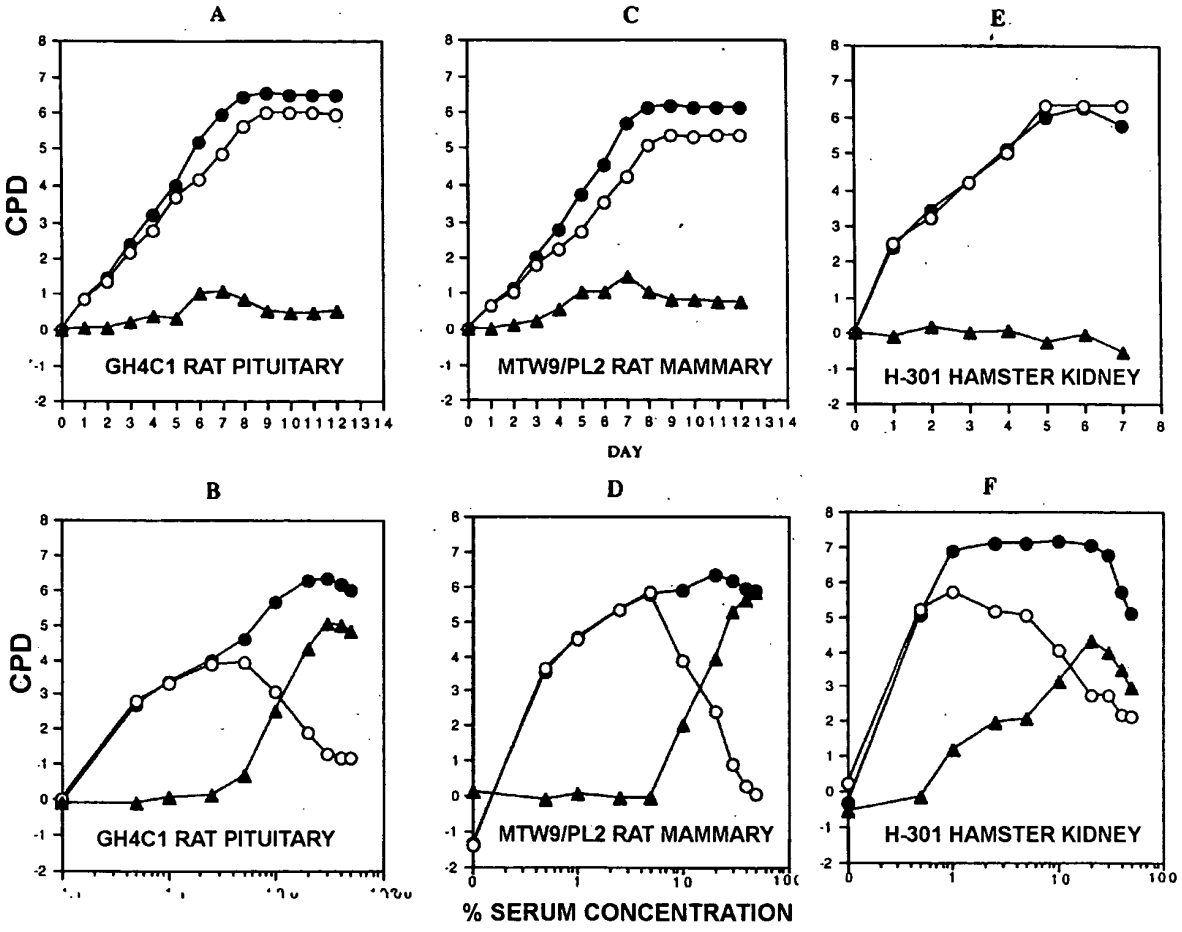
—○— NO STEROID

—●— + E_2

—□— + DHT

FIGURE 49

EFFECTS OF ESTROGEN ON STEROID HORMONE-RESPONSIVE RODENT TUMOR CELL GROWTH

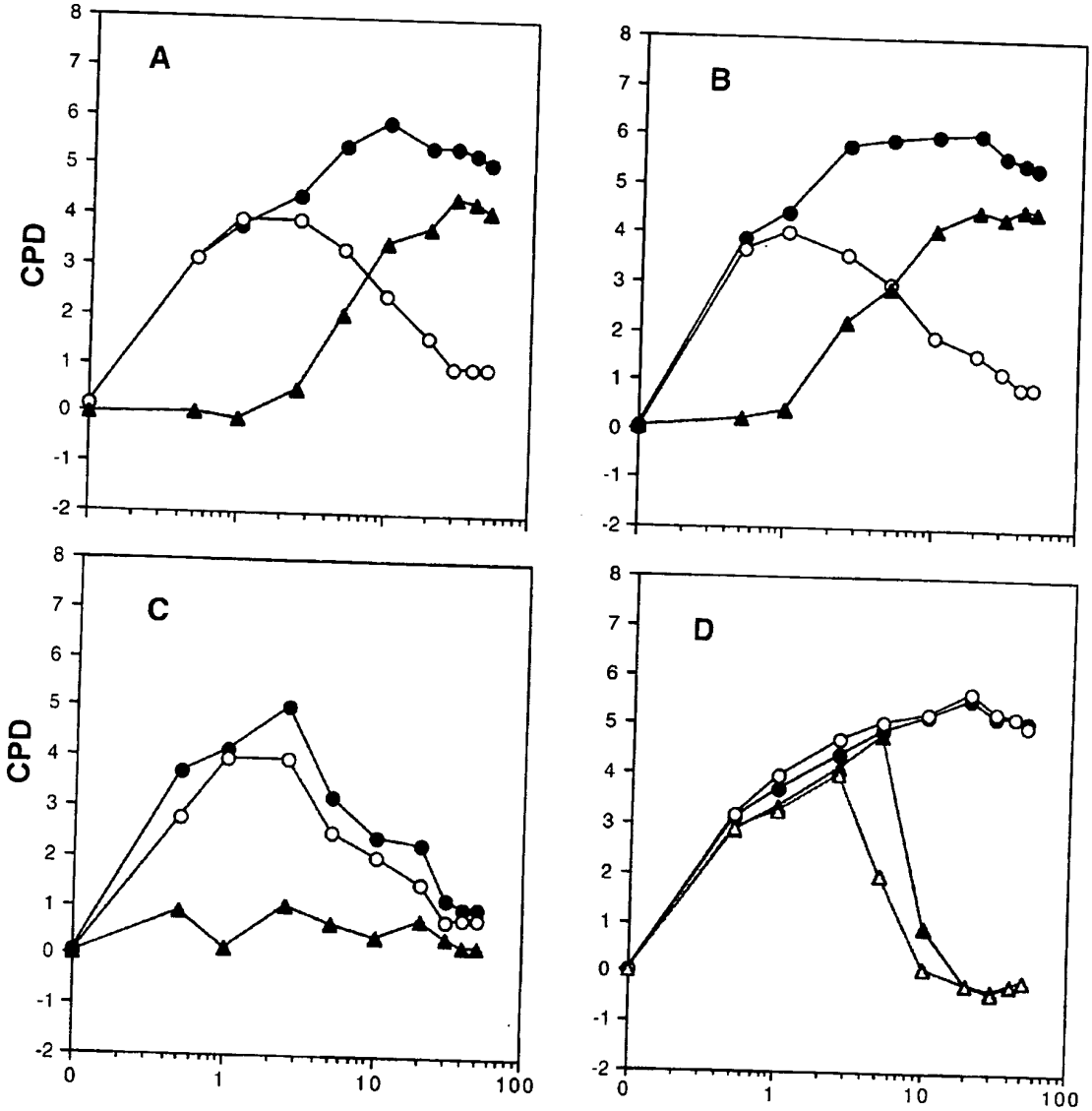


Comparison of the effects of estrogen on steroid hormone-responsive rodent tumor cell growth in serum-free defined medium and in D-MEM/F-12 supplemented with increasing concentrations of CDE horse serum.

(A) GH_4C_1 rat pituitary tumor cell growth measured daily in serum-free PCM-9 with E_2 (closed circles) and without E_2 (open circles). The estrogenic effect is shown by triangles. (B) GH_4C_1 cell growth measured after 9 d in D-MEM-F-12 supplemented with the designated concentrations of CDE horse serum with E_2 (closed circles) and without E_2 (open circles). The estrogenic effect is shown by triangles. (C) and (D) show the same experiments as in (A) and (B) respectively, but with th MTW9/PL2 rat mammary tumor cells. The serum-free medium in (D) was DDM-2A. (E) and (F) show the same xperiments as in (A) and (B), resp ctively, except with the H-301 hamster kidney tumor cells. In (E) the serum-free m dium was CAPM.

FIGURE 50

THE EFFECT OF DHT, E_2, AND DES ON LNCaP CELLS GROWN IN CDE HORSE SERUM



% SERUM CONCENTRATION

LEGEND:

(A) Open circles = - DHT
Closed circles = + DHT
Closed trianges = Androgenic effect

(B) Open circles = - E_2
Closed circles = + E_2
Closed triangles = Estrogenic eff ct

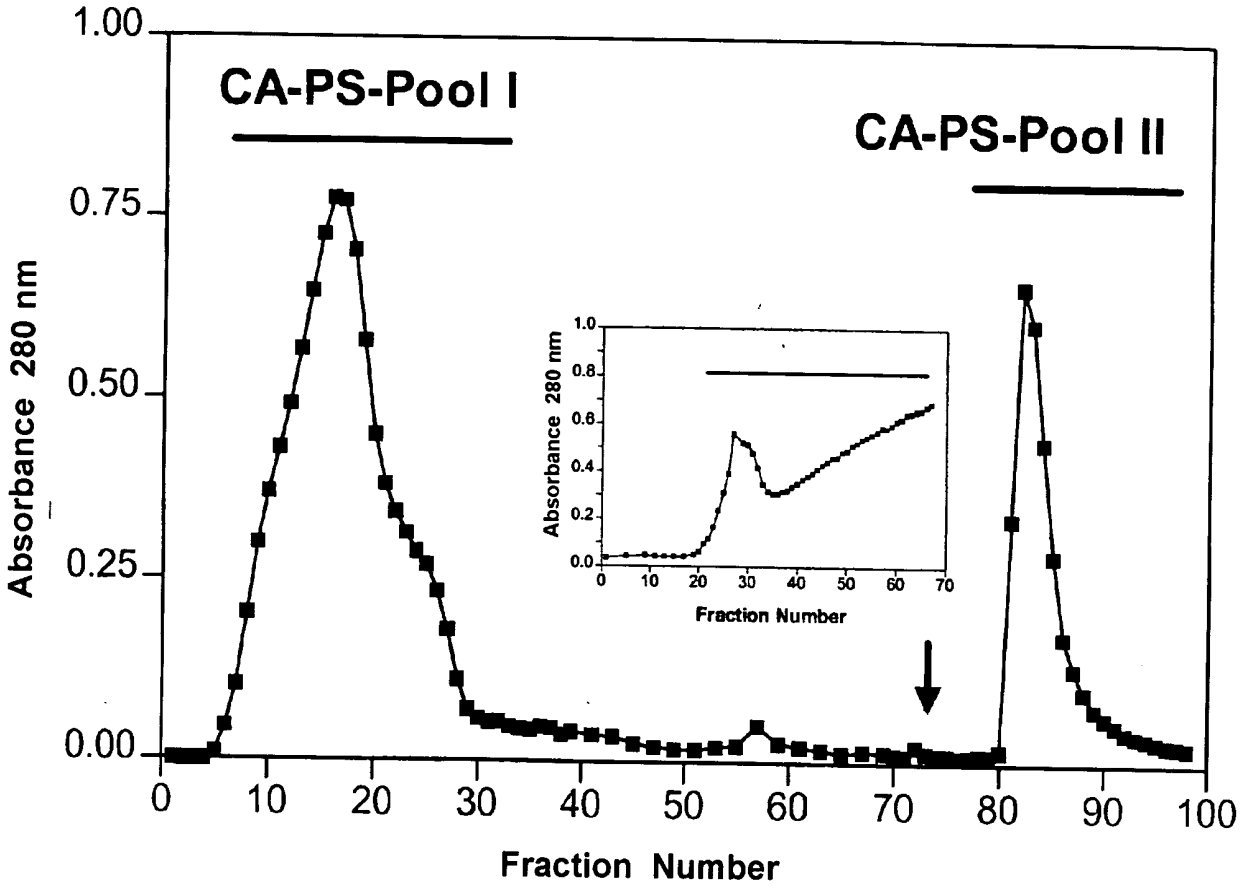
(C) Open circles = - DES
Closed circles = + DES
Closed triangles = Estrogenic effect

(D) Open circles = DHT & DES
Closed circles = E_2 & DES
Open triangles = No additions
Closed triangles = DES only

FIGURE 51

PHENYL SEPHAROSE ELUTION OF

CBG (CA-PS-POOL 1) AND SHBG-LIKE (CA-PS-POOL 11)



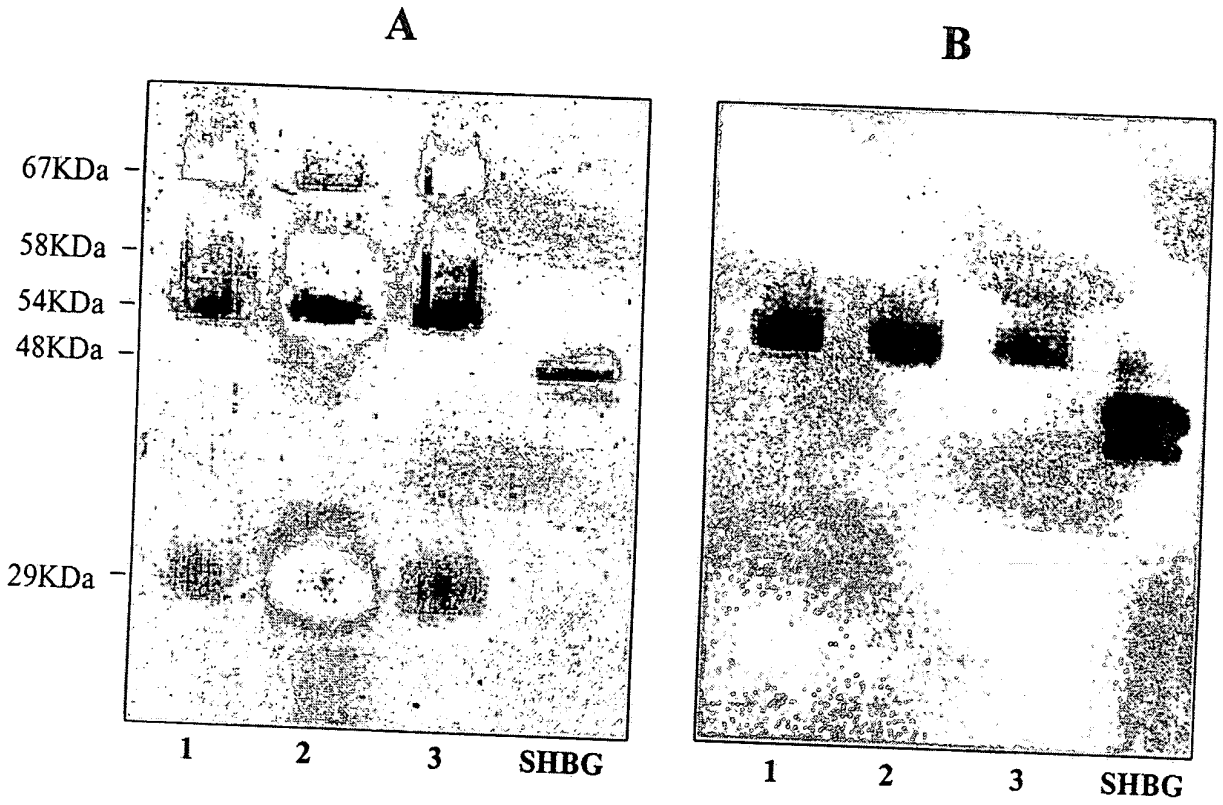
ARROW = ELUTION WITH 40% ETHYLENE GLYCOL

INSERT: CORTISOL AFFINITY COLUMN ELUTION

BARS = POOLED ACTIVE FRACTION

FIGURE 52

SDS PAGE (A) AND WESTERN ANALYSIS (B) OF THREE PREPARATIONS OF CA-PS-POOL II VS HUMAN SHBG

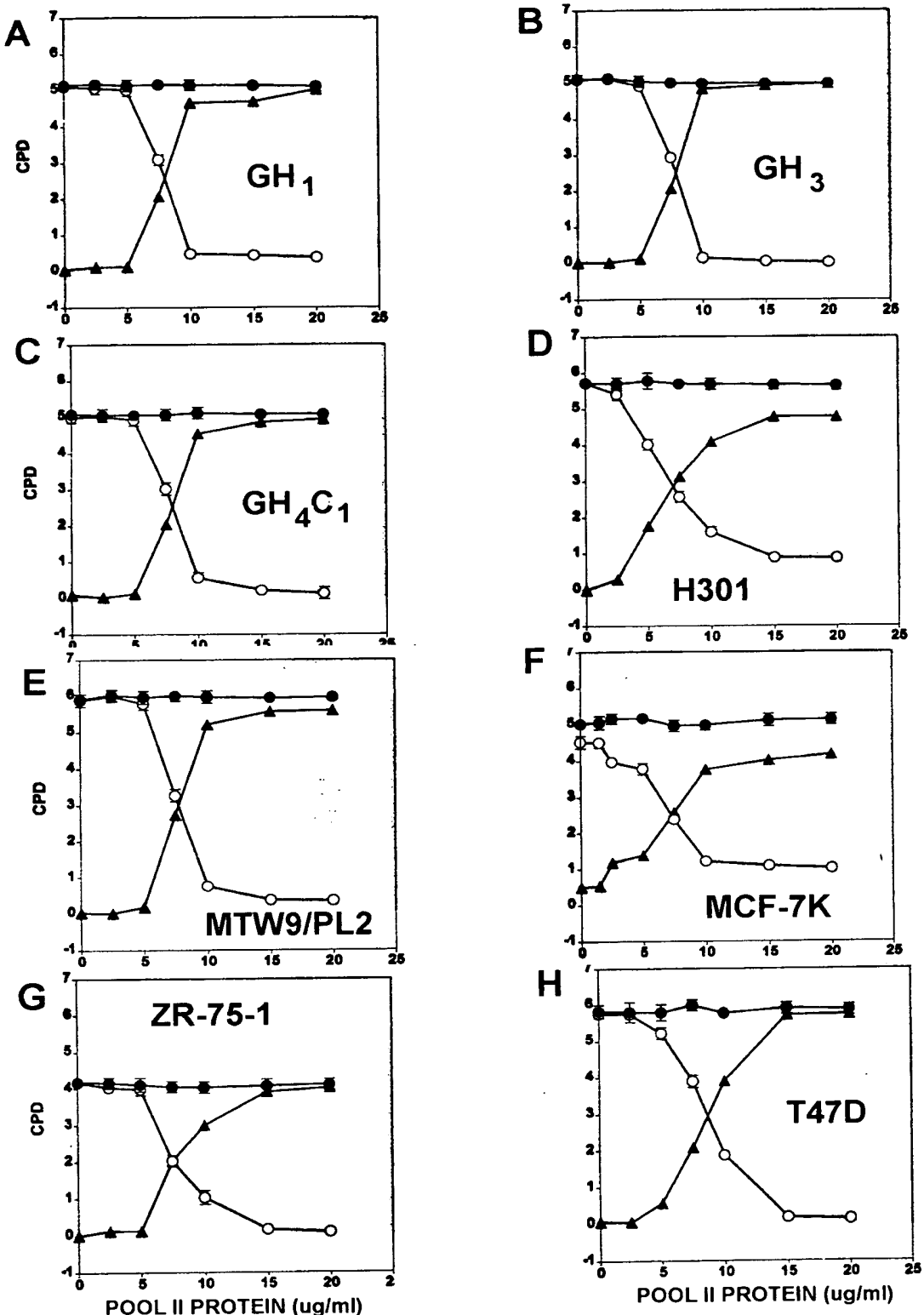


LANES 1, 2, AND 3 = 10 ug each of CA-PS-POOL II

LANE "SHBG" = 10 mg of purified protein

FIGURE 53

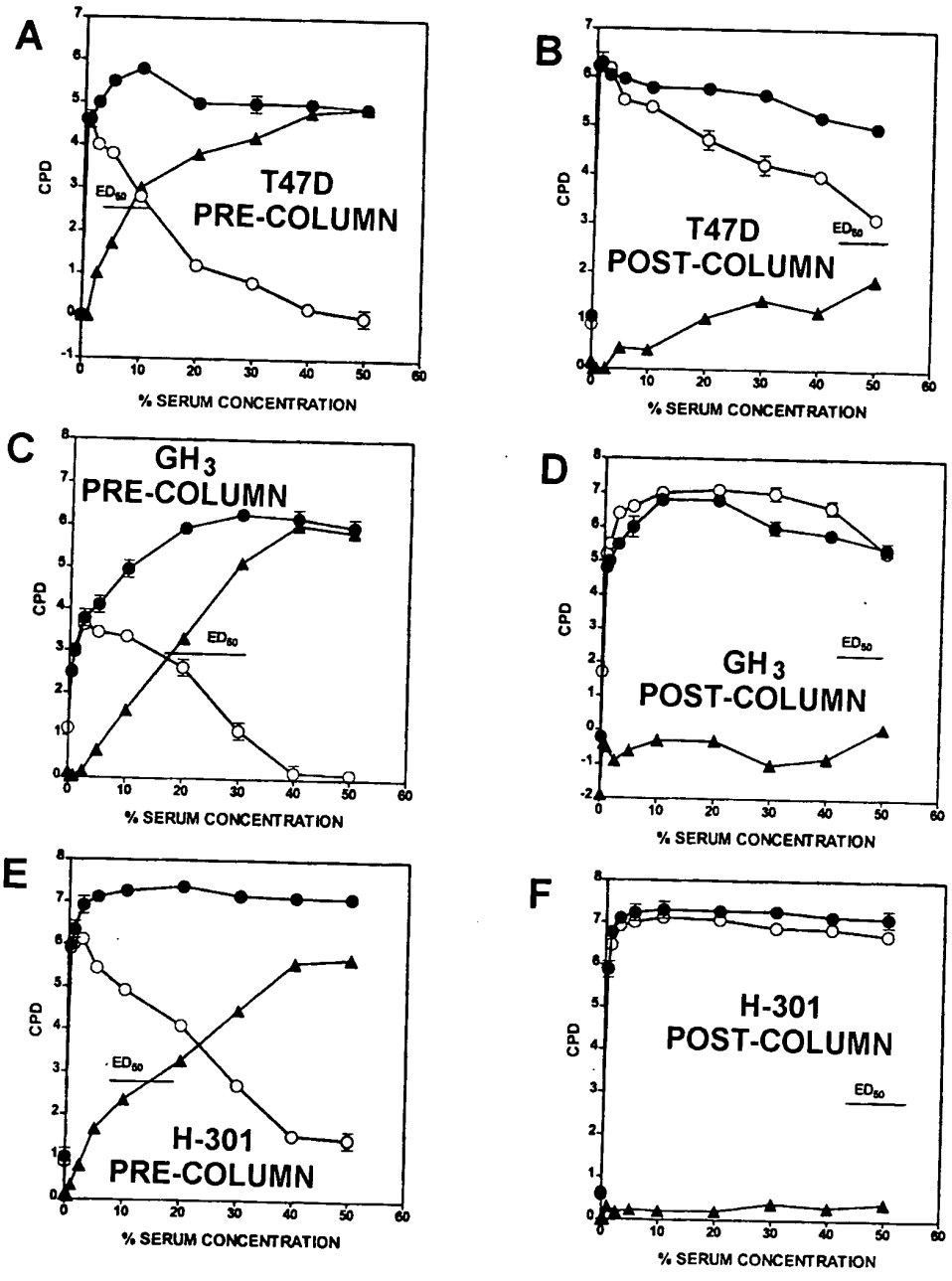
ASSAY OF CA-PS-POOL II ESTROGEN REVERSIBLE INHIBITORY ACTIVITY WITH SEVERAL ER$^+$CELL LINES



LEGEND:
Open circles = $-E_2$
Clos d circles = $+E_2$
Closed triangl s = Estrog nic effect

FIGURE 54

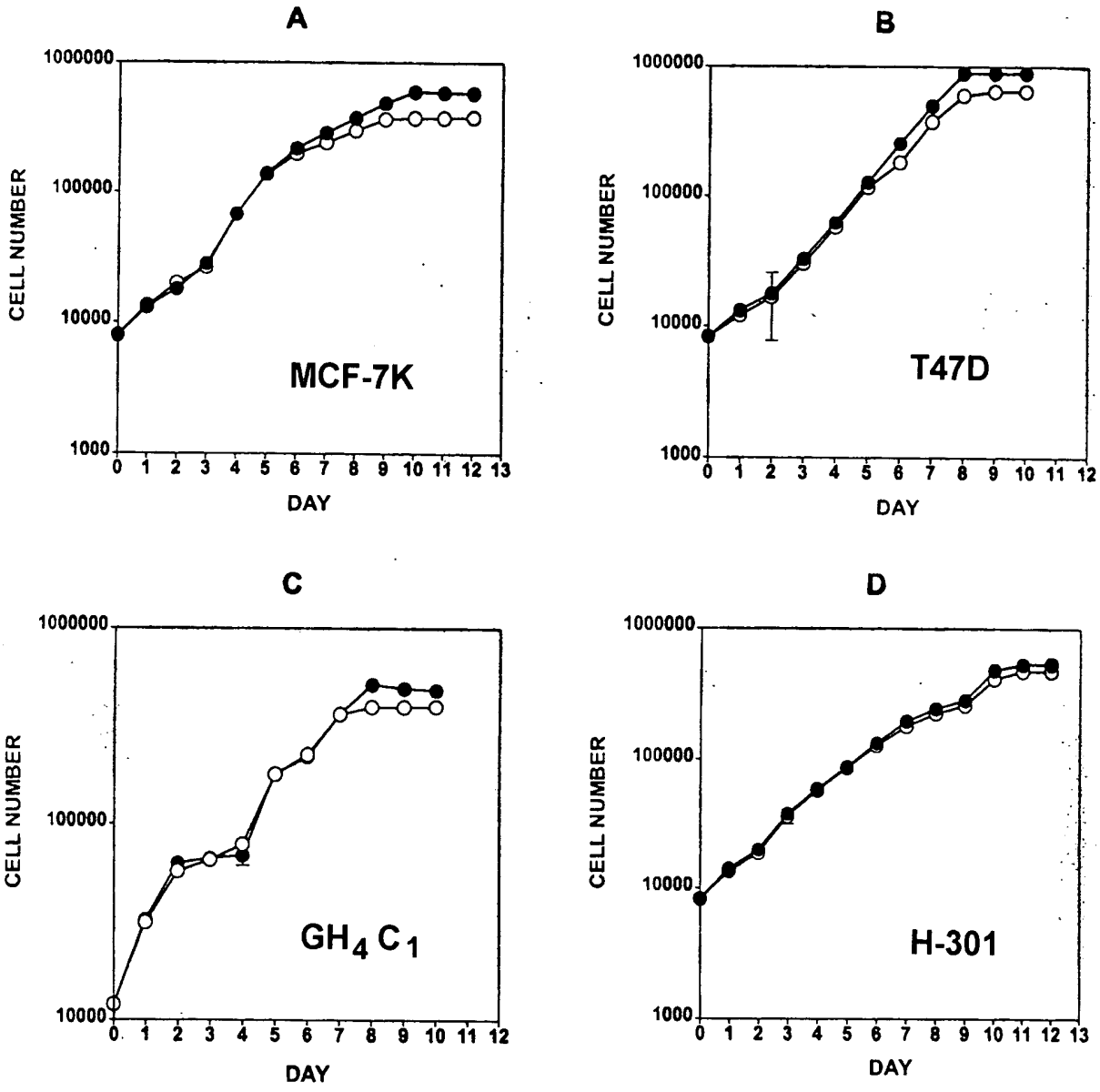
CORTISOL-AGAROSE AFFINITY REMOVAL OF THE INHIBITOR FROM CDE-SERUM



LEGEND: Open circles = $-E_2$
Closed circles = $+E_2$
Closed triangles = Estrogenic effect

FIGURE 55

GROWTH OF ER+ CELL LINES IN SERUM-FREE MEDIUM ± E_2



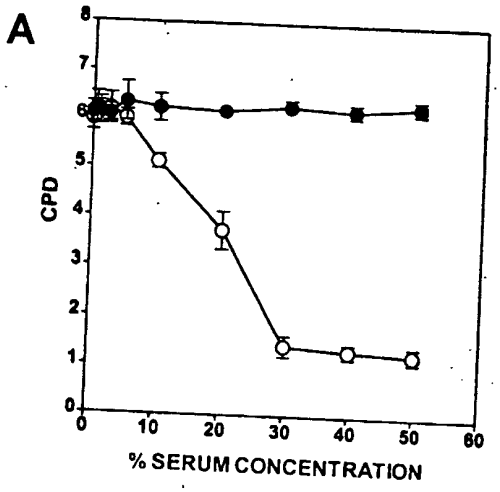
LEGEND:

Closed circles = + E_2

Open circles = – E_2

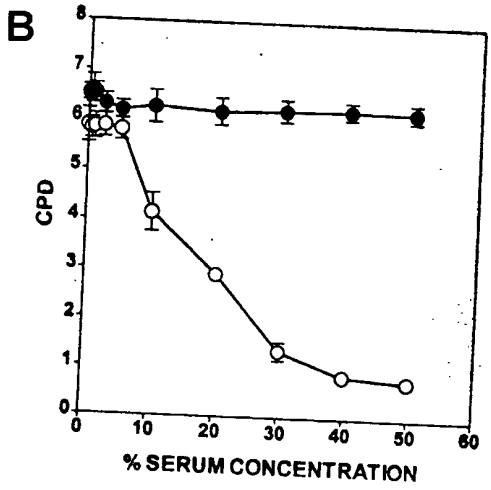
FIGURE 56

EFFECT OF CDE-SERUM ON ESTROGEN RESPONSIVE GROWTH OF THREE ER$^+$ CANCER CELL LINES IN SFM



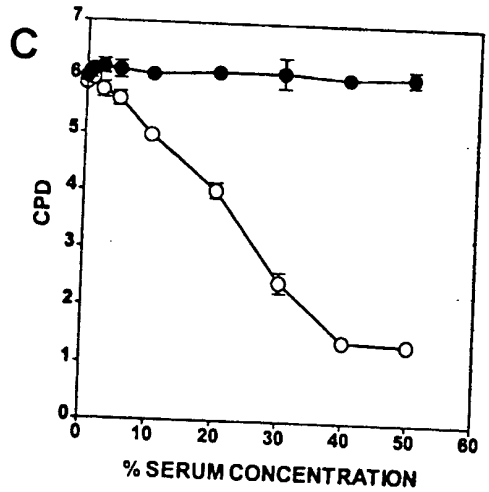
A =

T47D IN DDM-2MF



B =

MTW9/PL2 IN DDM-2A

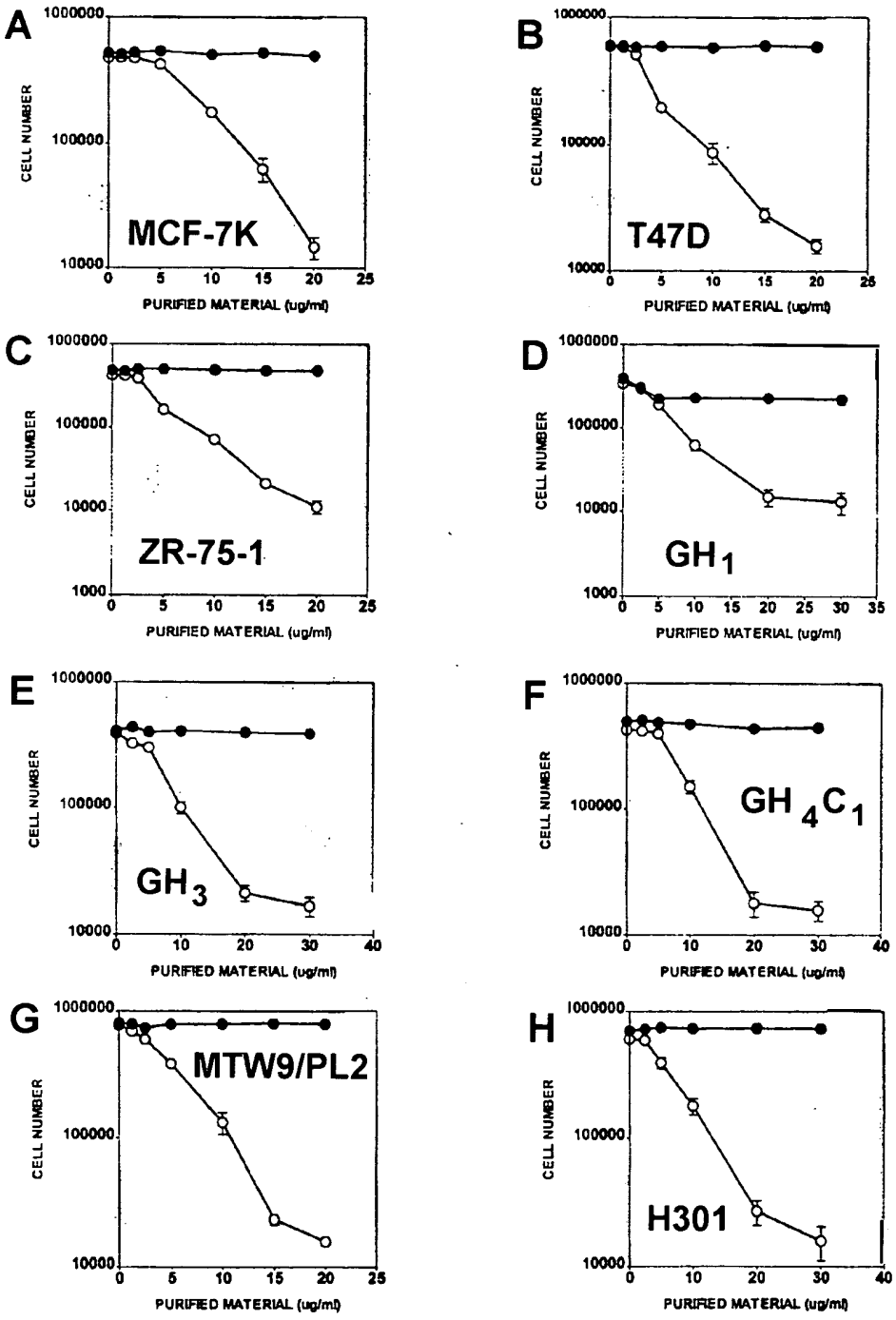


C =

GH_4C_1 IN PCM 9

FIGURE 57

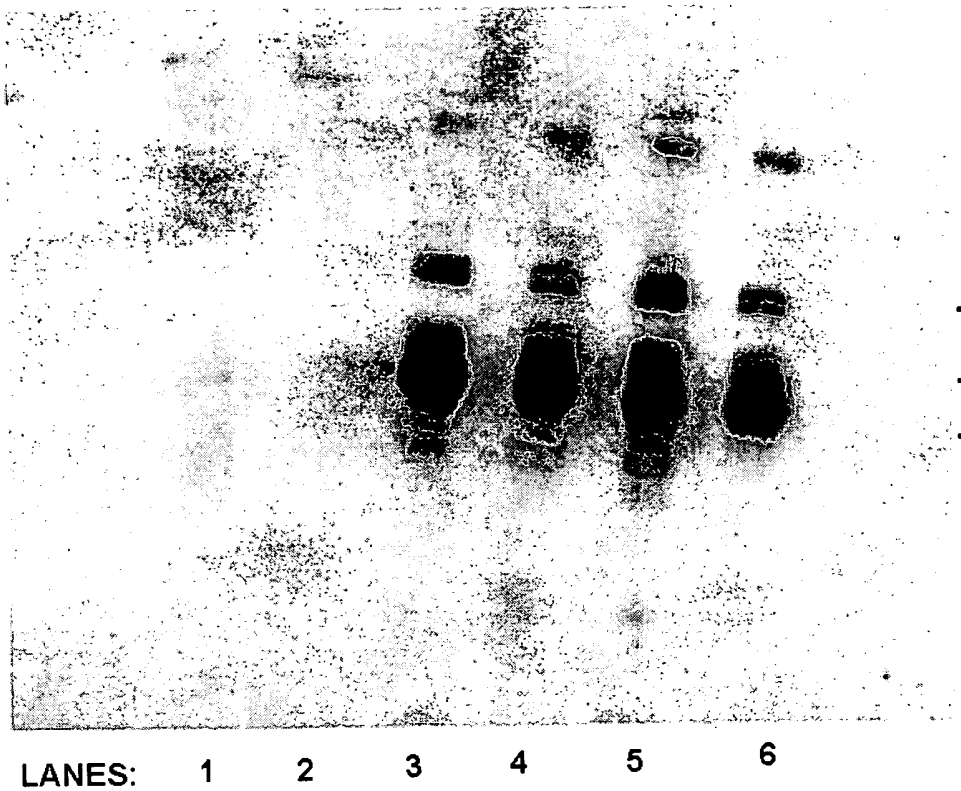
EFFECT OF CA-PS-POOL II ON ESTROGEN RESPONSIVE GROWTH IN SERUM FREE MEDIUM



LEGEND: Open circles = $-E_2$
Closed circles = $+E_2$

FIGURE 58

WESTERN ANALYSIS OF CBG (POOL I) AND SHBG (POOL II) PREPARATION WITH ANTI-54 kDa



1 = CBG PREPARATION #5

2 = CBG PREPARATION #6

3 = SHBG PREPARATION #5.1

4 = SHBG PREPARATION #5.2

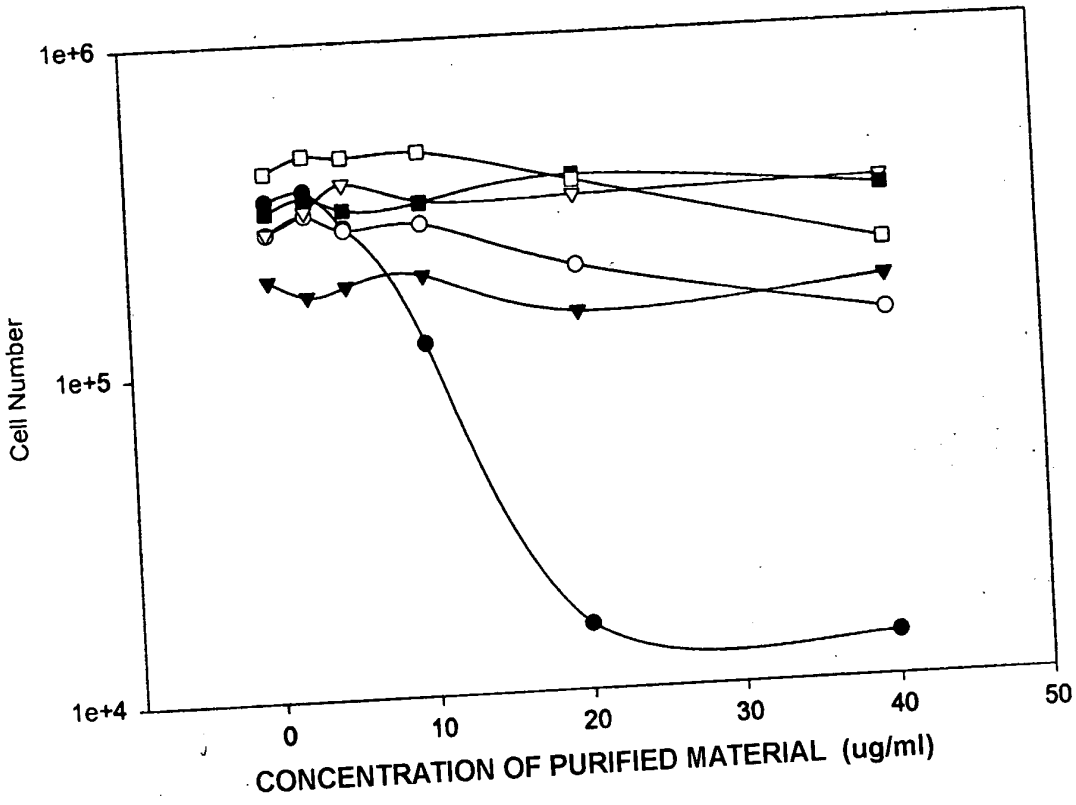
5 = SHBG PREPARATION #6.1

6 = SHBG PREPARATION #6.2

ANTIBODY = RABBIT ANTI-54 kDa 1:5000 DILUTION

FIGURE 59

EFFECT OF ANTI-54kDa ANTISERUM ON MTW9/PL2 CELLS GROWN IN THE PRESENCE OF CA-PS-POOL II



LEGEND:

- No antibody
- Antibody 1:5000
- Antibody 1:1000
- Antibody 1:500
- Antibody 1:100
- Antibody 1:50

FIGURE 60

WESTERN BLOT OF COMMERCIAL PREPARATIONS OF HORSE IgA, IgG AND IgM WITH THE ANTI-54 kDa ANTIBODY

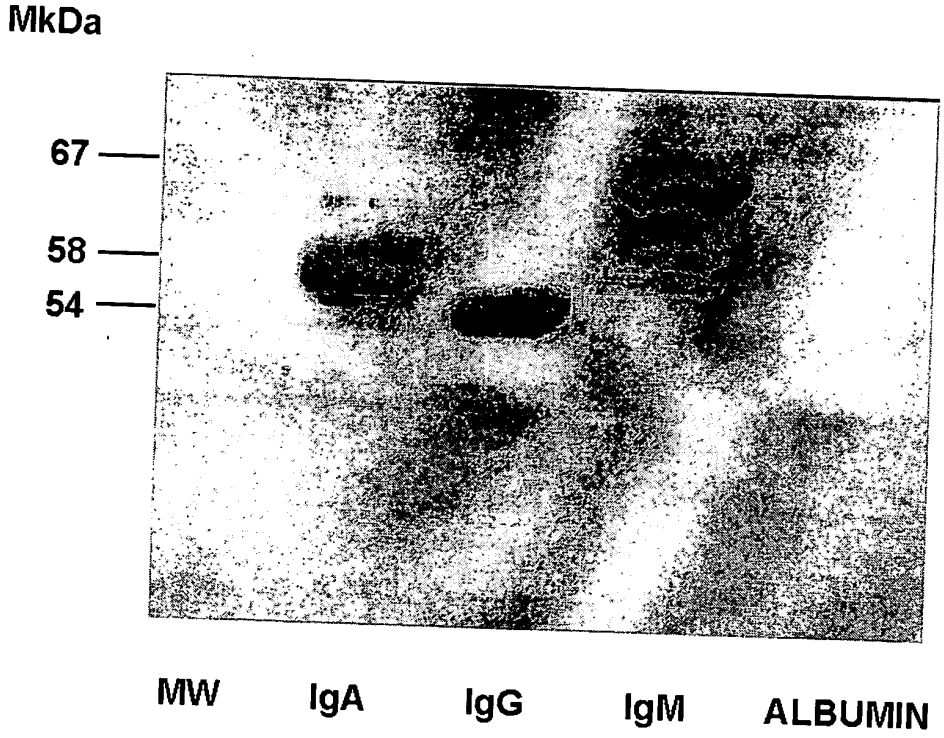


FIGURE 61

EFFECT OF COMMERCIALLY PURIFIED HORSE IgG ON MTW9/PL2 CELL GROWTH IN 2.5% CDE-HORSE SERUM

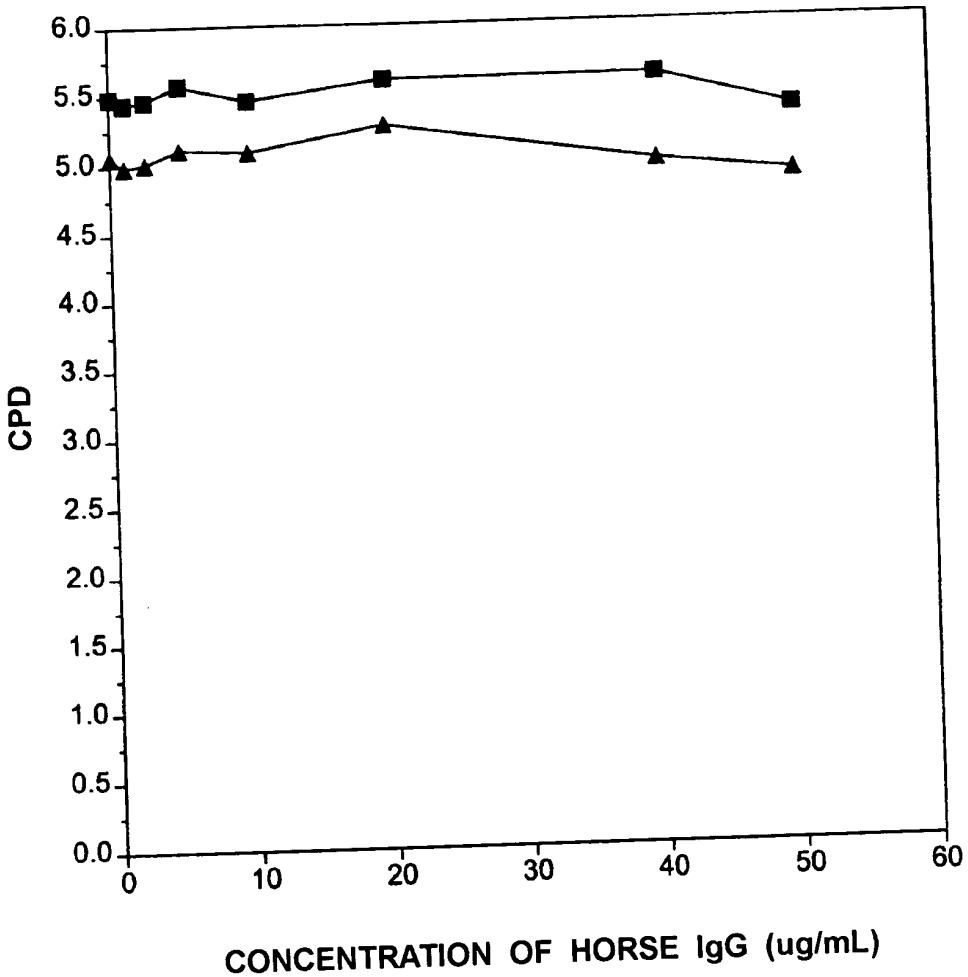
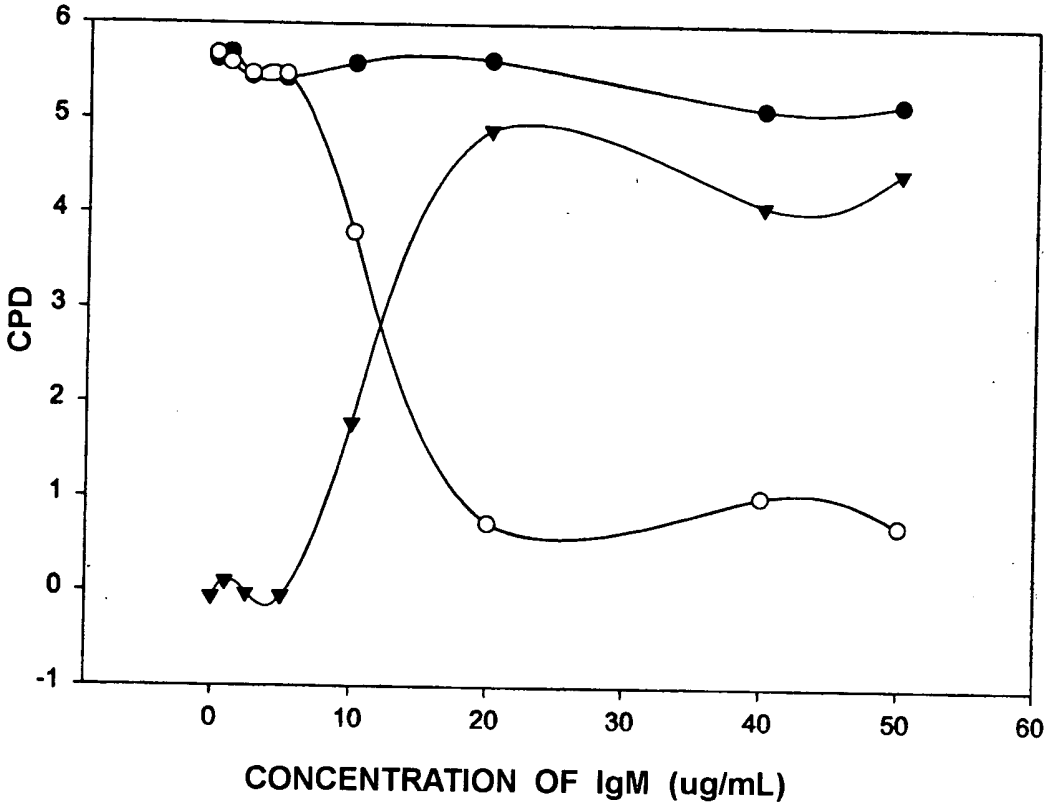


FIGURE 62

EFFECT OF HORSE IgM ON GROWTH OF THE MTW9/PL2 CELLS IN 2.5% CDE HORSE SERUM $\pm E_2$



LEGEND:

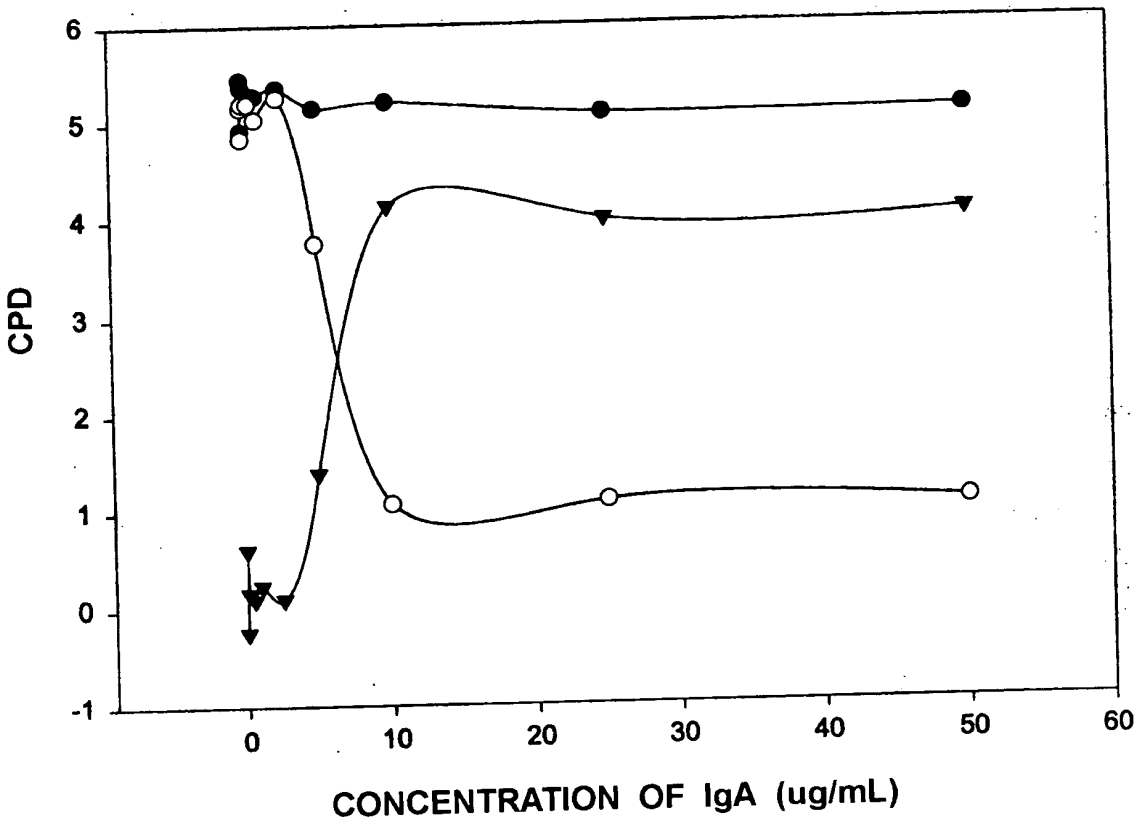
● = + E_2

○ = − E_2

▼ = Estrogenic effect

FIGURE 63

EFFECT OF HORSE IgA ON GROWTH OF THE MTW9/PL2 CELLS IN 2.5% CDE HORSE SERUM $\pm E_2$



LEGEND:

—●— = + E_2

—○— = − E_2

—▼— = Estrogenic effect

FIGURE 64

SDS PAGE AND WESTERN ANALYSIS OF RAT "SHBG-LIKE" PREPARATIONS

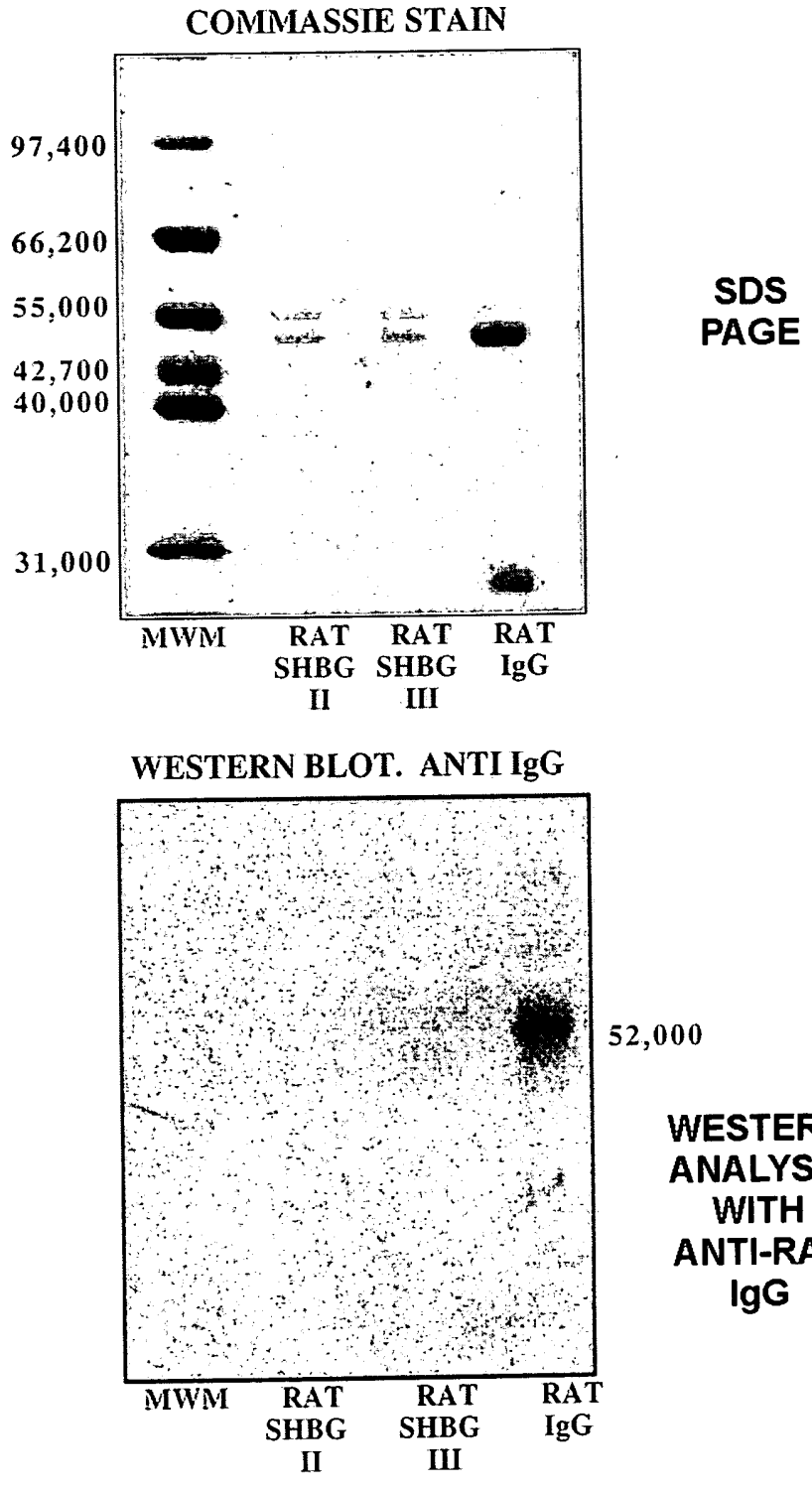


FIGURE 65

CROSSREACTION OF THE PURIFIED RAT "SHBG-LIKE" PROTEINS WITH ANTI- IgA, IgG1 AND IgM MONOCLONAL ANTIBODIES

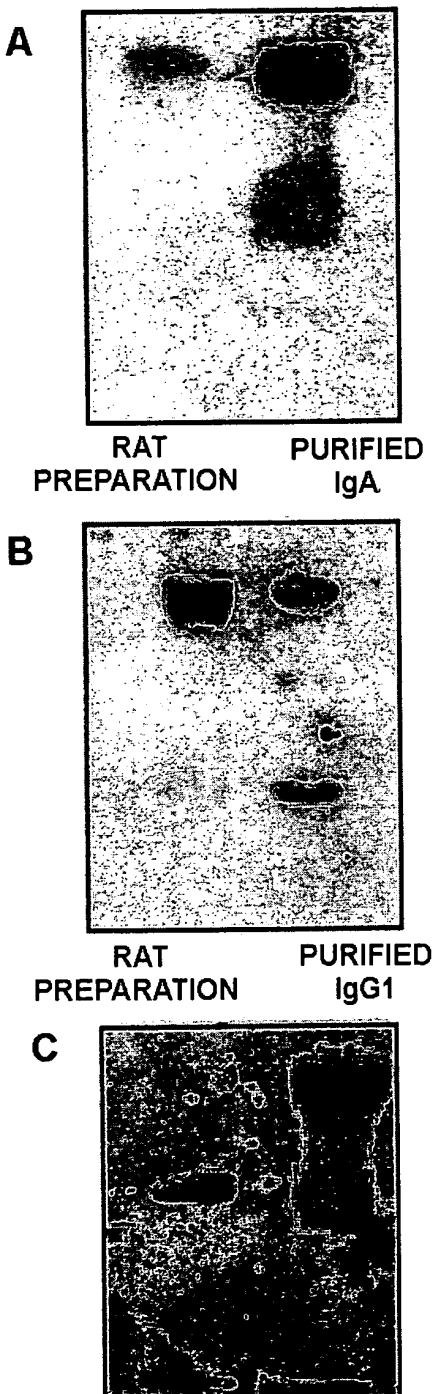
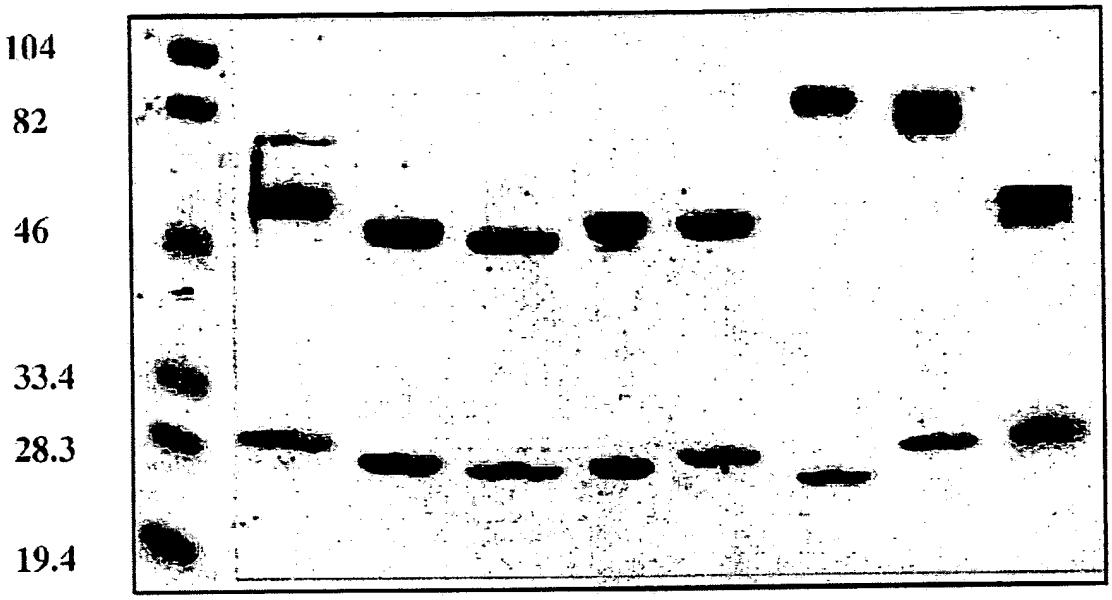


FIGURE 66

SDS PAGE (A) AND WESTERN ANALYSIS (B) WITH ANTI-SHBG AND RAT Ig'S

A KDa

RAT Igs COMMASSIE STAINED



B

RAT Igs WESTERN BLOT. ANTI SHBG ANTIBODY KDa

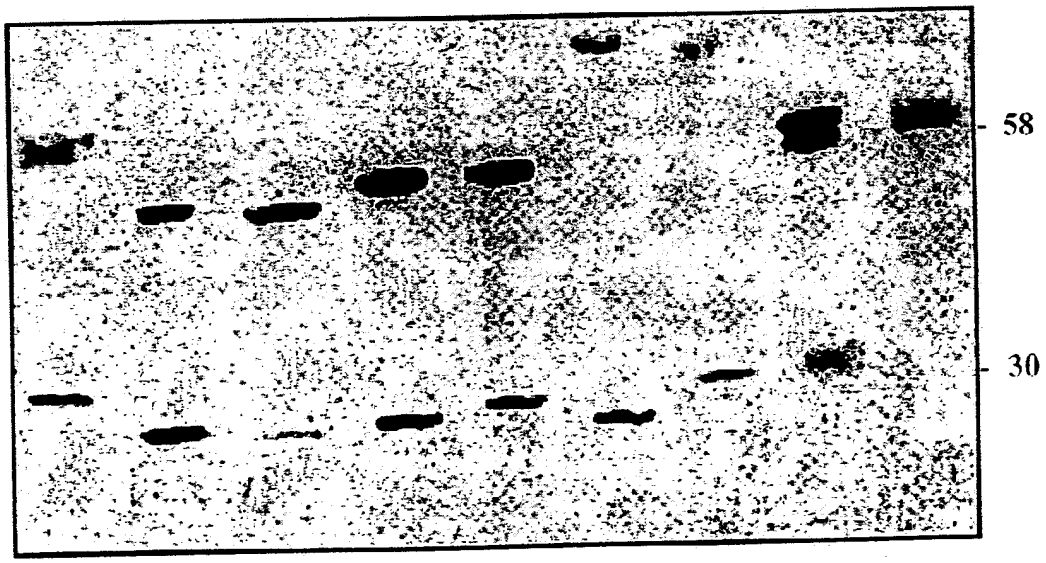
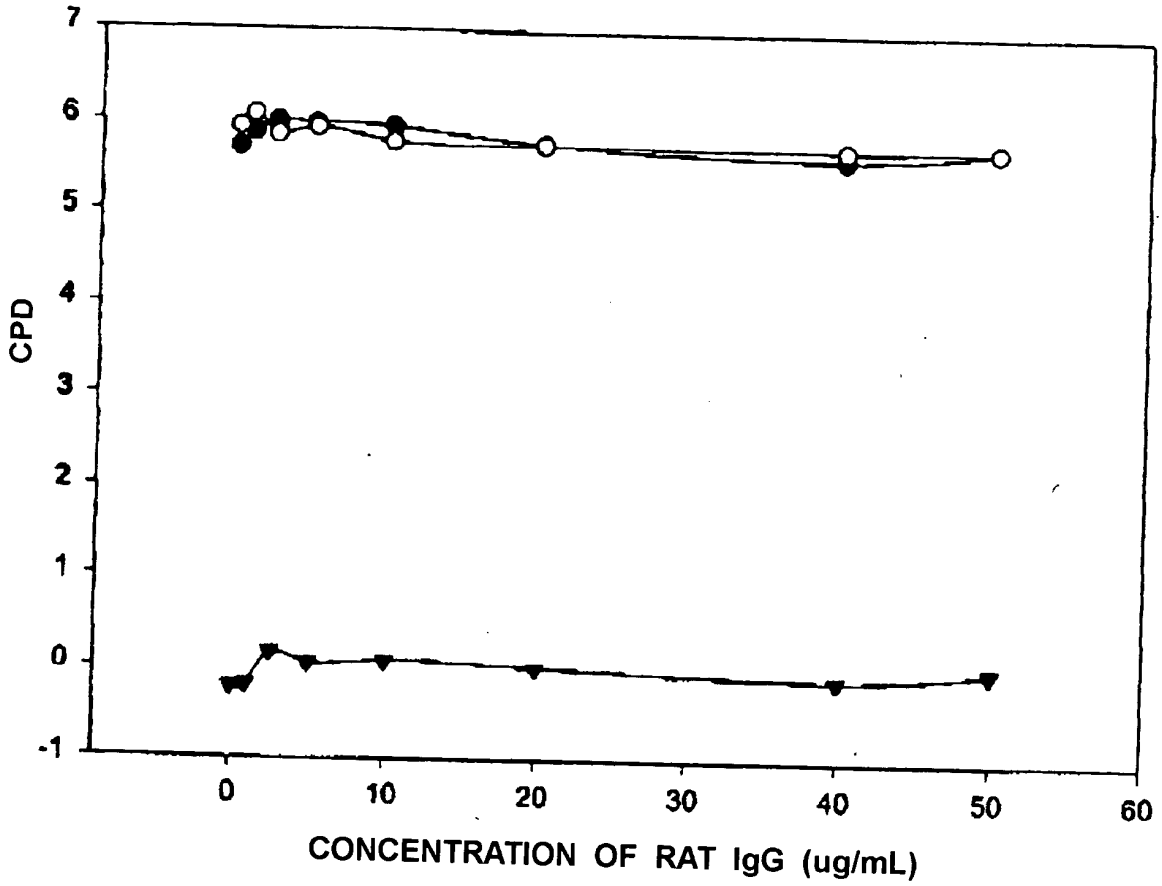


FIGURE 67

EFFECT OF RAT IgG ON MTW9/PL2 CELL GROWTH IN 2.5% CDE RAT SERUM



LEGEND:

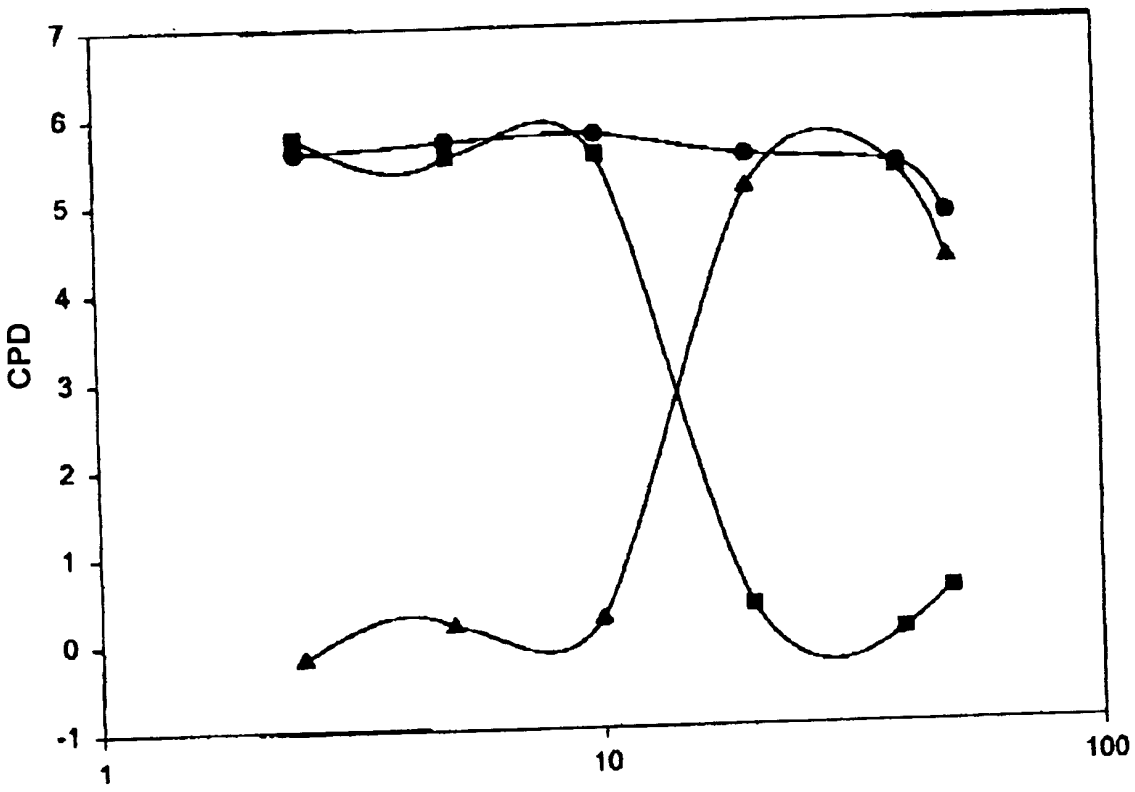
Closed circles = + E_2

Open circles = – E_2

Closed triangles = Estrogenic effect

FIGURE 68

EFFECT OF RAT IgA ON MTW9/PL2 CELL GROWTH IN 2.5% CDE RAT SERUM



LEGEND:

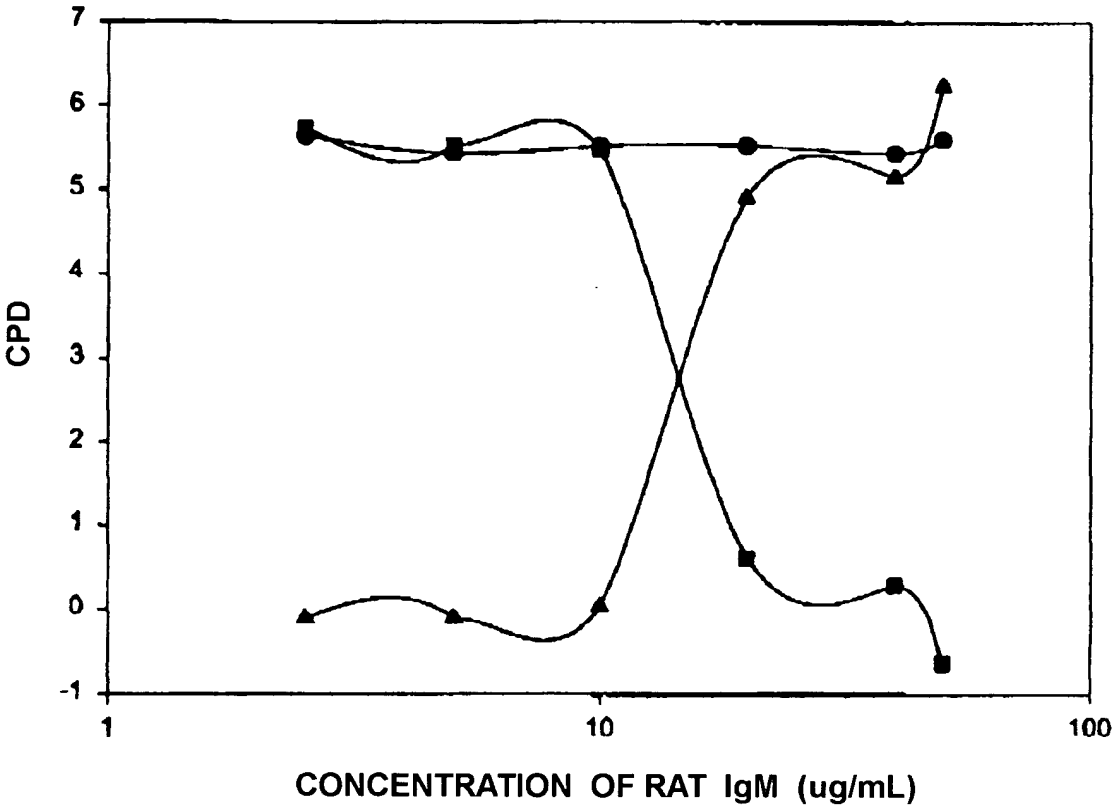
Closed circles = + E_2

Closed squares = − E_2

Closed triangles = Estrogenic effect

FIGURE 69

EFFECT OF RAT IgM ON MTW9/PL2 CELL GROWTH IN 2.5% CDE RAT SERUM



LEGEND:

Closed squares = − E_2

Closed circles = + E_2

Closed triangles = Estrogenic effect

FIGURE 70

ELUTION OF IgM FROM MANNAN BINDING PROTEIN COLUMN

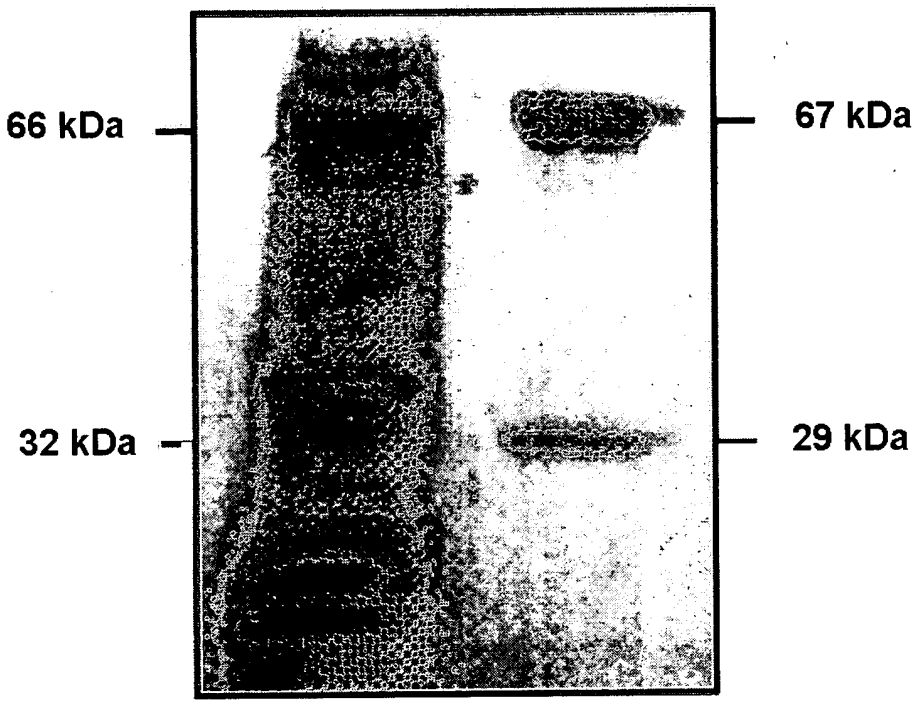
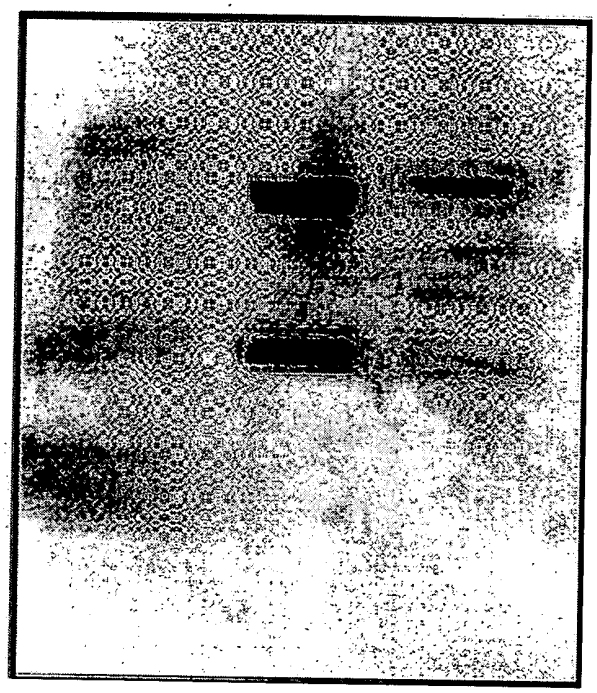


FIGURE 71

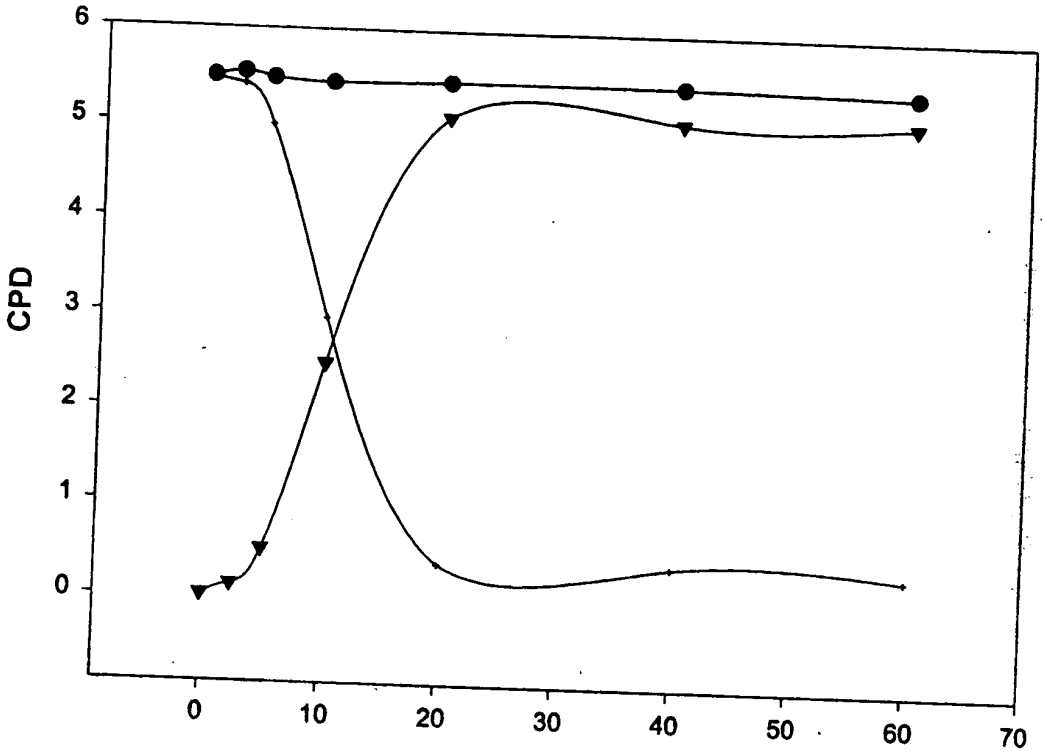
IgM PURIFICATION FROM PLASMA BY JACALIN



MW HUMAN IgA PURIFIED IgA

FIGURE 72

EFFECT OF IgM ISOLATED FROM HUMAN PLASMA ON MTW9/PL2 GROWTH IN SERUM-FREE CONDITIONS



LEGEND:

—●— = + E_2

—•— = − E_2

—▼— = Estrogenic effect

FIGURE 73

THE EFFECT OF VARIOUS IgA AND IgM PREPARATIONS ON MTW9/PL2 CELLS GROWN IN SERUM-FREE MEDIUM

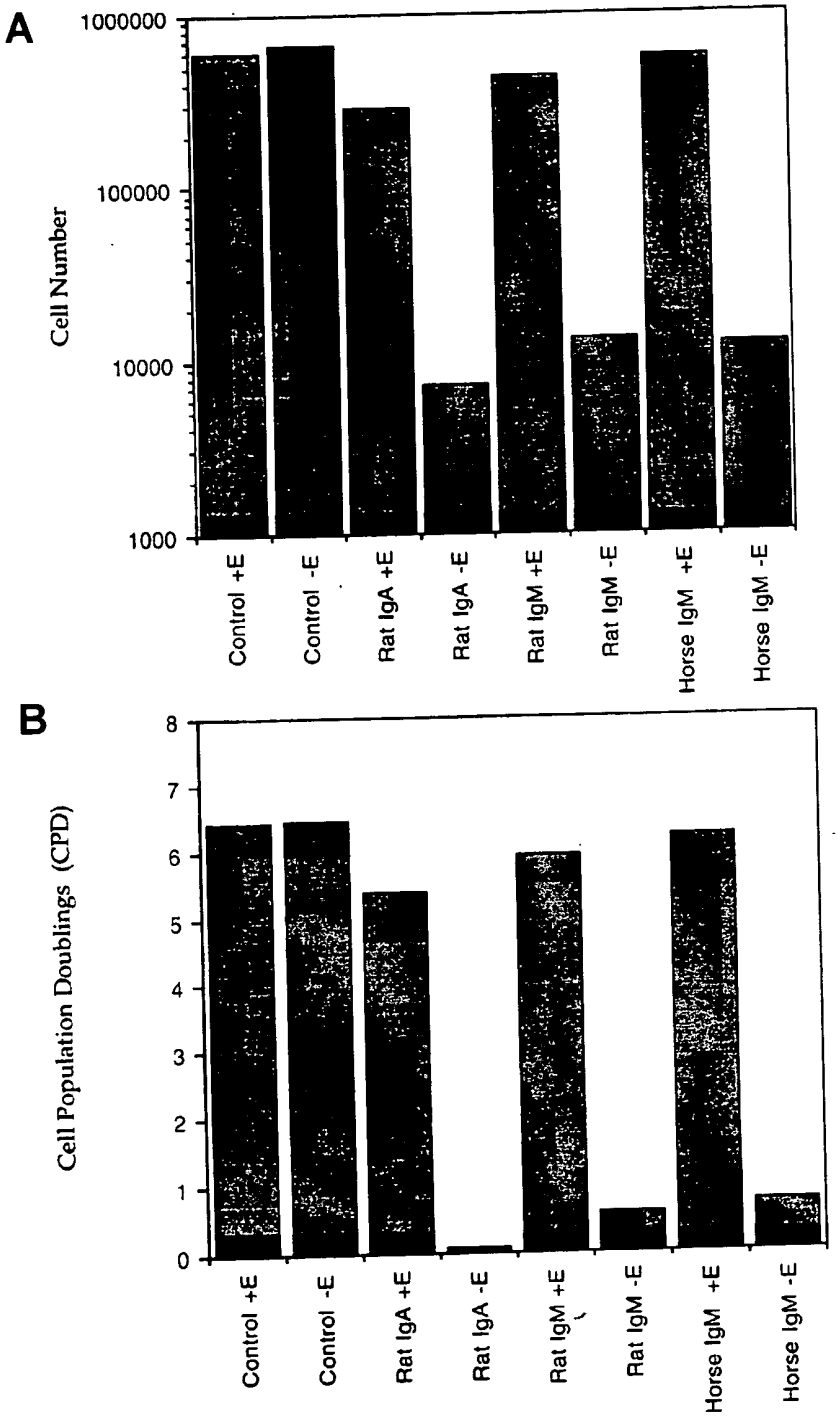
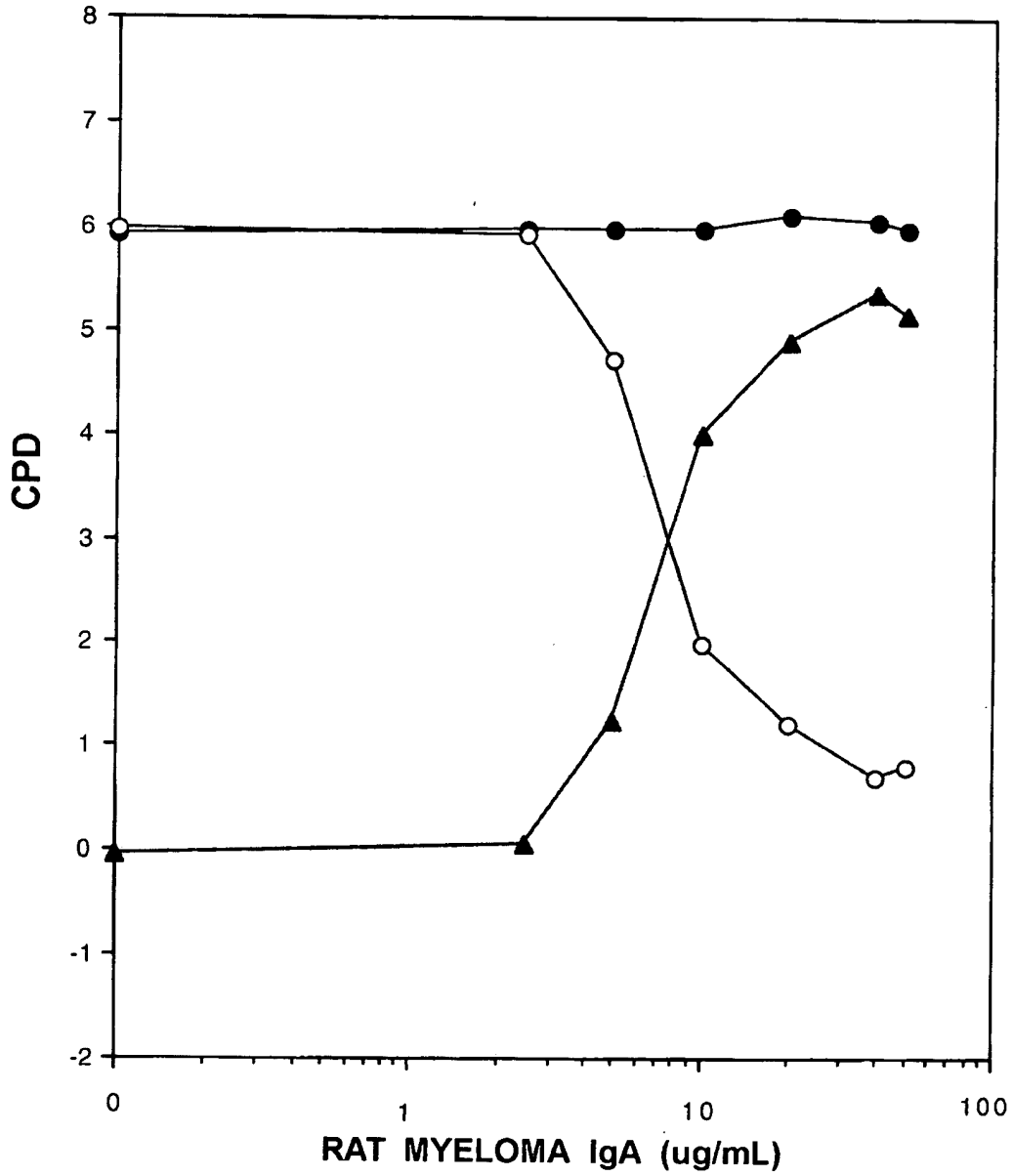


FIGURE 74

RAT MYELOMA IgA TITRATION ON GH_1 CELLS GROWN IN SERUM-FREE CONDITIONS



LEGEND:

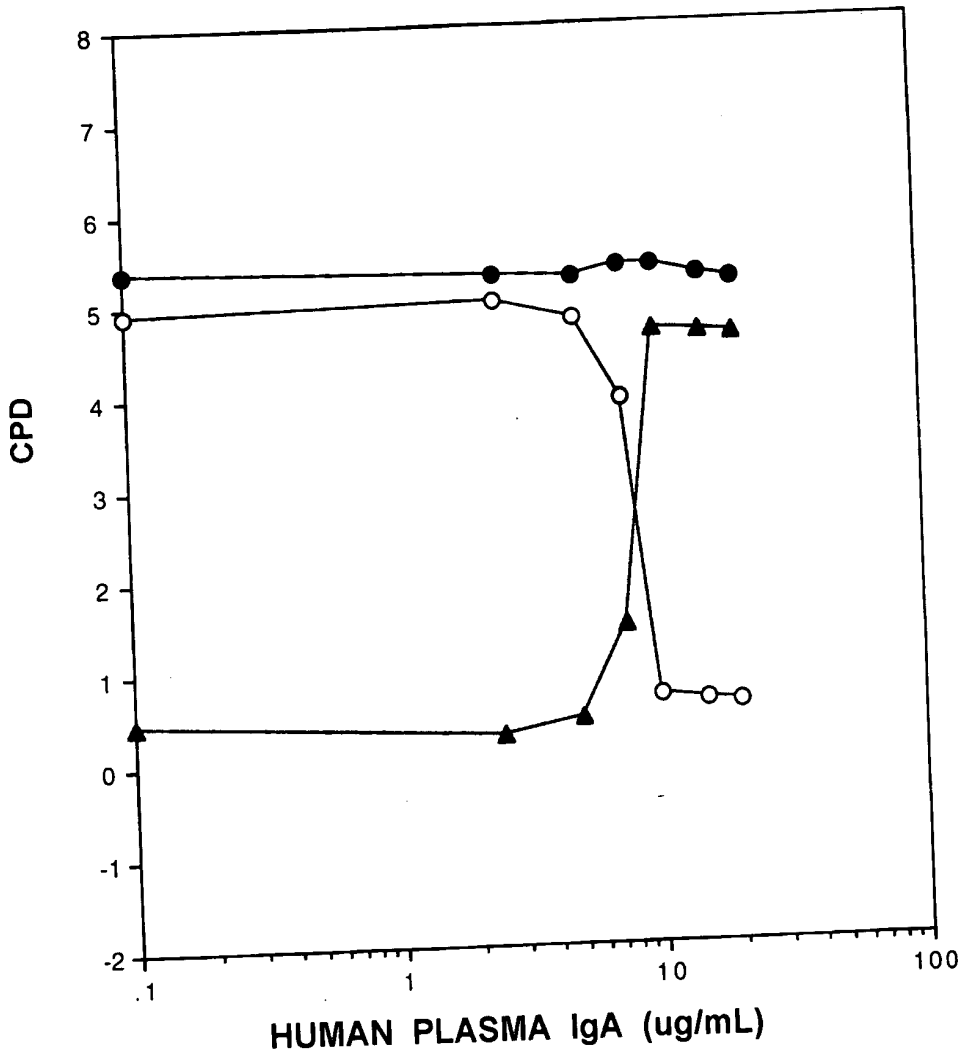
Closed circles = + E_2

Open circles = – E_2

Closed triangles = Estrogenic effect

FIGURE 75

HUMAN PLASMA IgA TITRATION ON GH_1 CELLS GROWN IN SERUM-FREE CONDITIONS



LEGEND:

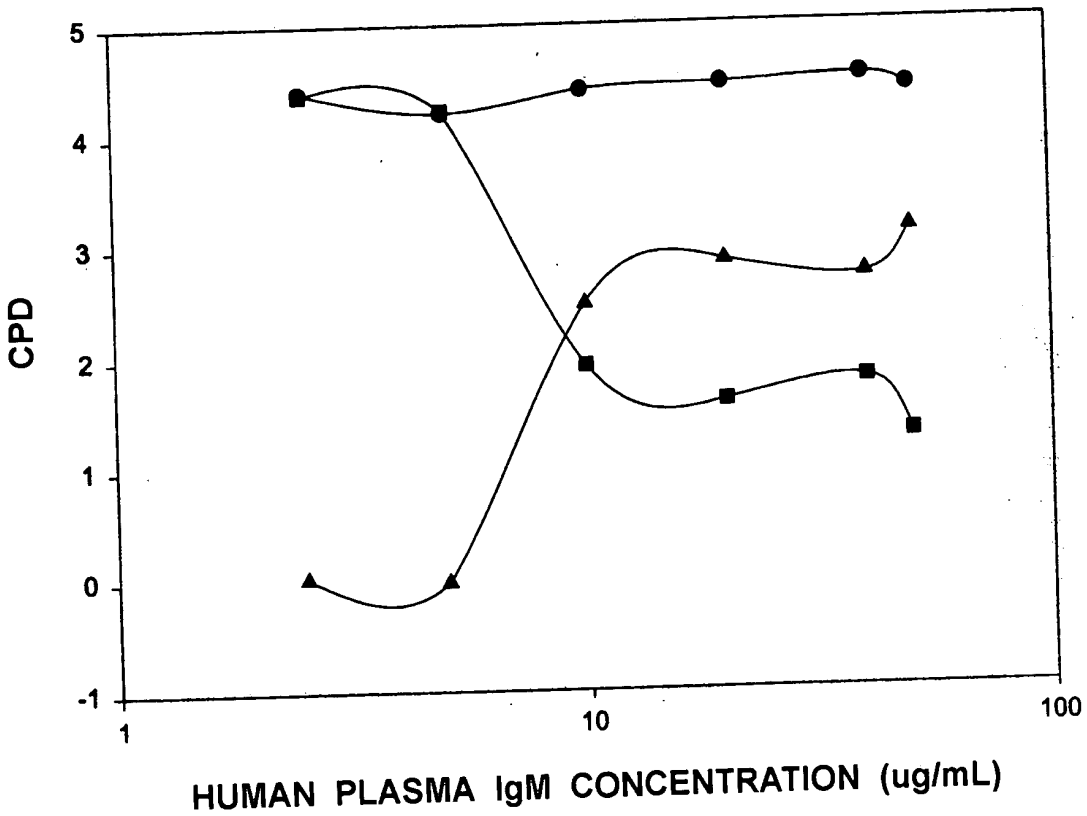
Closed circles = + E_2

Open circles = − E_2

Closed triangles = Estrogenic effect

FIGURE 76

HUMAN PLASMA IgM TITRATION ON GH_1 CELLS GROWN IN SERUM-FREE CONDITIONS



LEGEND:

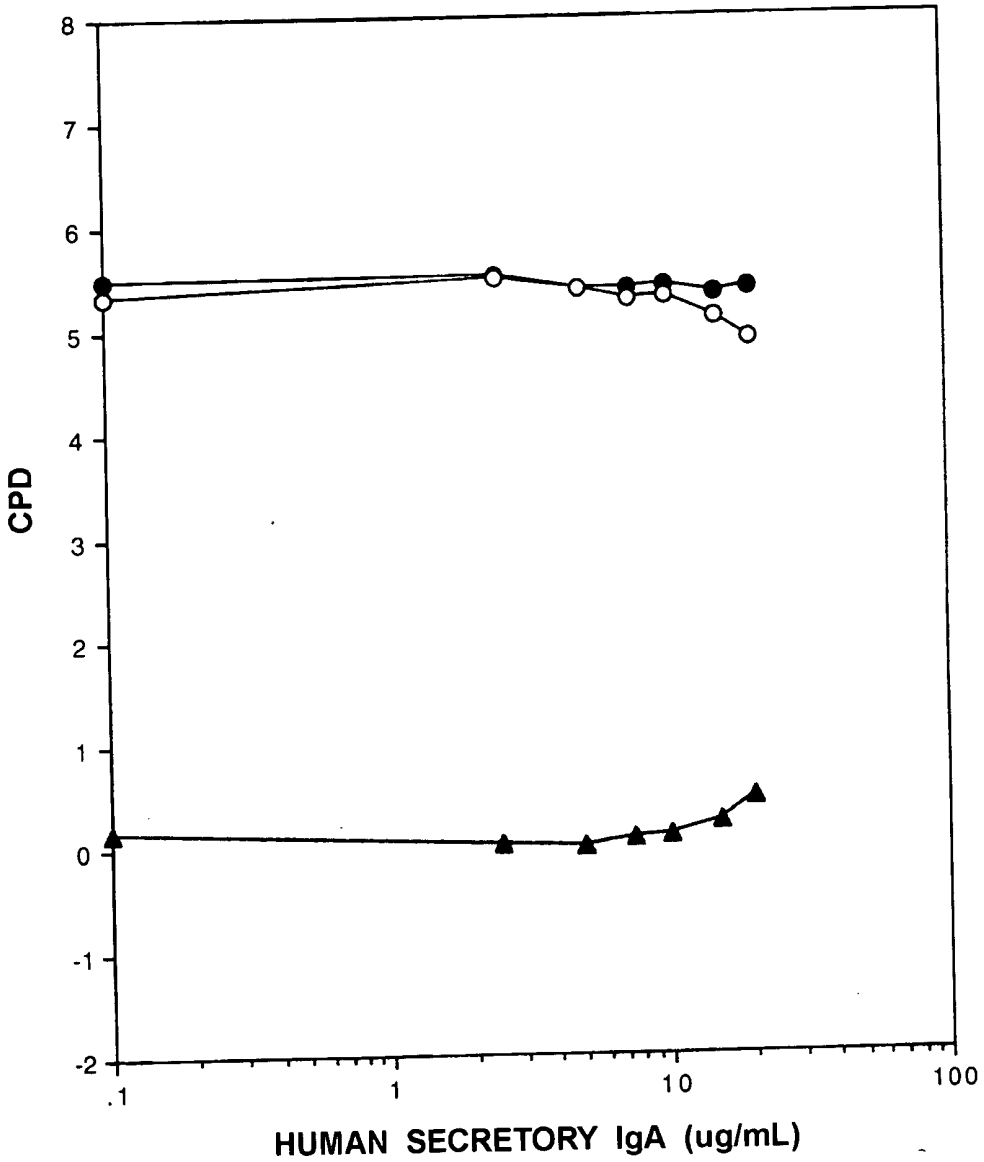
—●— = + E_2

—■— = − E_2

—▲— = Estrogenic effect

FIGURE 77

EFFECT OF HUMAN SECRETORY IgA ON GH_1 CELLS GROWN IN SERUM-FREE CONDITIONS



LEGEND:

Closed circles = + E_2

Open circles = − E_2

Closed triangles = Estrogenic effect

FIGURE 78

MECHANISM OF TRANSCYTOSIS OF IgA AND IgM BY MUCOSAL EPITHELIAL CELLS

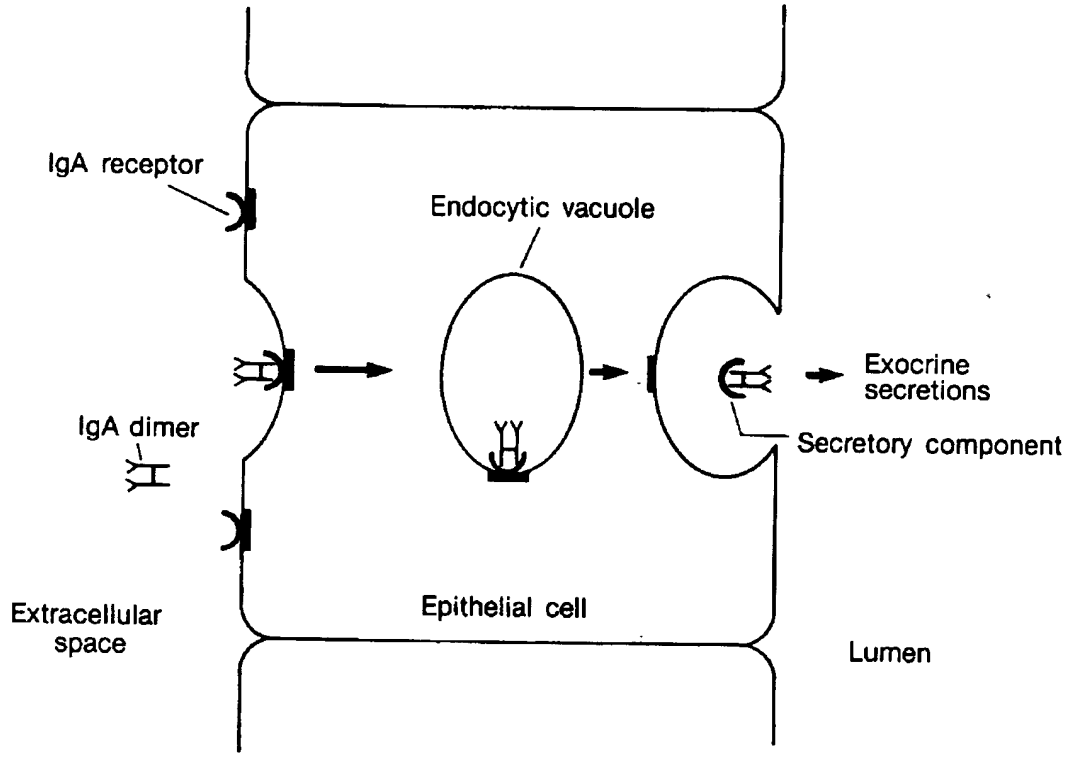
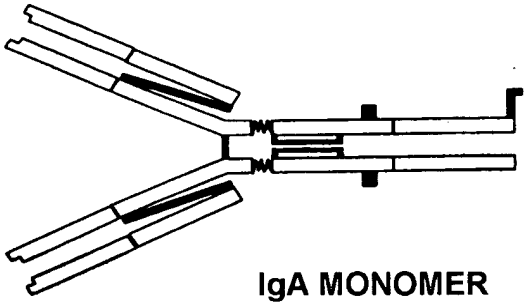


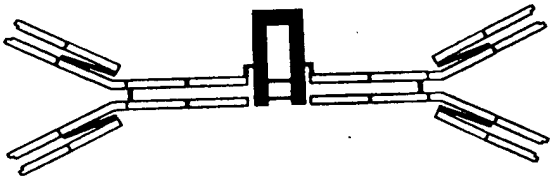
FIGURE 79

ESSENTIAL STRUCTURES OF HUMAN PLASMA AND SECRETORY IgA



IgA MONOMER (INACTIVE)

J CHAIN



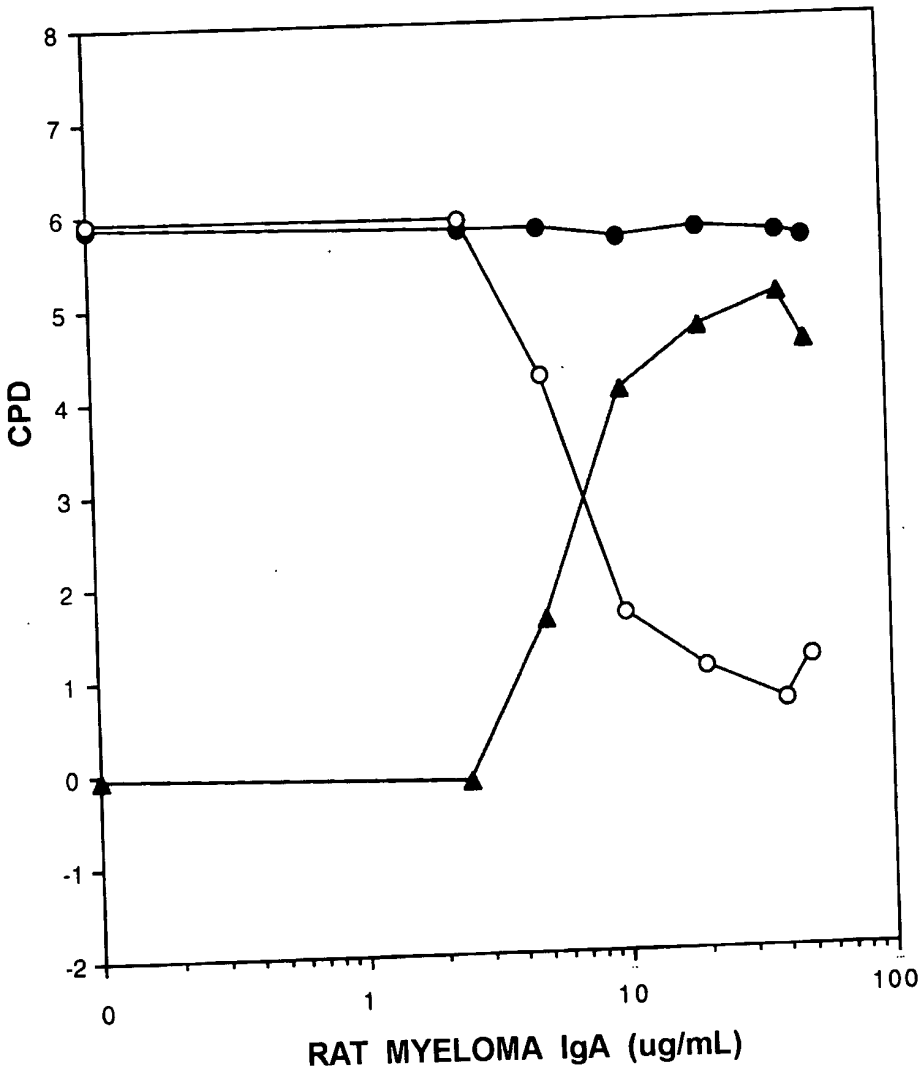
IgA DIMER WITH ATTACHED J CHAIN (ACTIVE)

SECRETORY PIECE OR SECRETORY COMPONENT (80% POLY-IgR)

SECRETORY IgA SHOWING J CHAIN AND SECRETORY COMPONENT (INACTIVE)

FIGURE 80

EFFECT OF RAT MYELOMA IgA ON GH_3 CELLS GROWN IN SERUM-FREE MEDIUM



LEGEND:

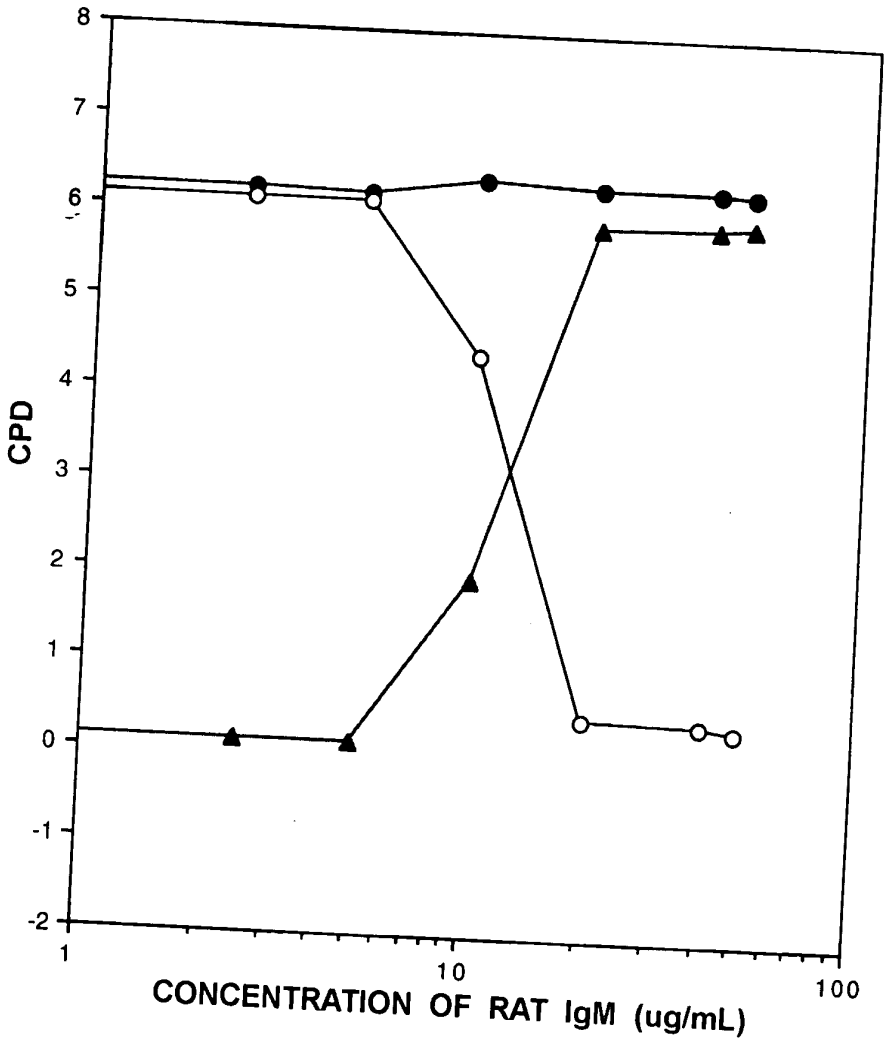
Closed circles = + E_2

Open circles = − E_2

Closed triangles = Estrogenic effect

FIGURE 81

EFFECT OF RAT IgM ON GH_3 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

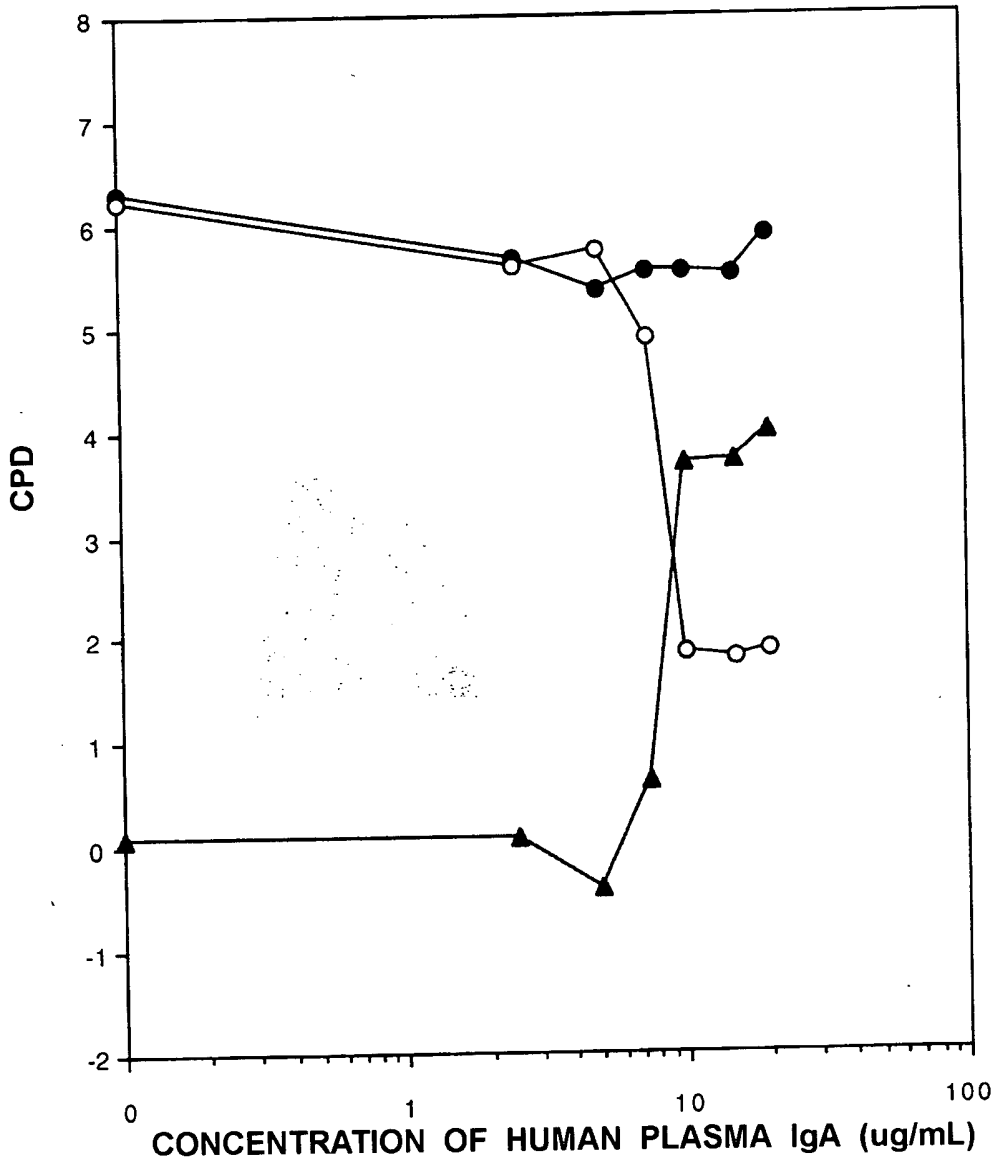
● = + E_2

○ = – E_2

▲ = Estrogenic effect

FIGURE 82

EFFECT OF HUMAN PLASMA IgA ON GH_3 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

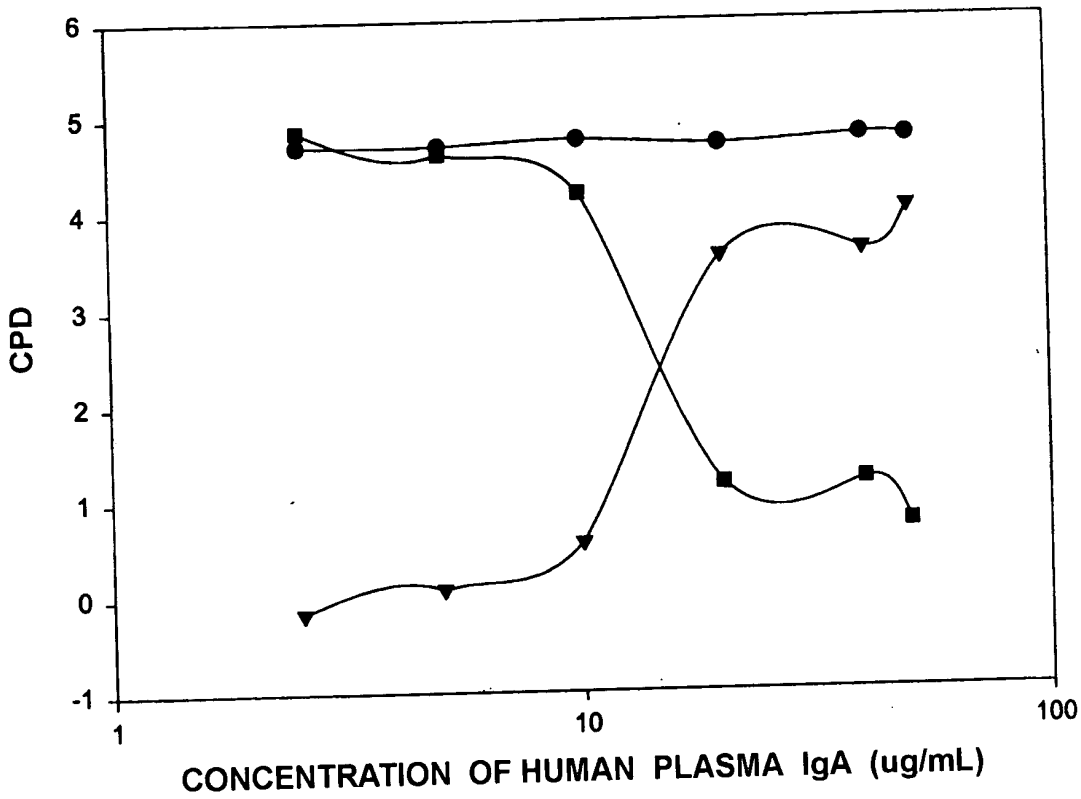
Closed circles = + E_2

Open circles = − E_2

Closed triangles = Estrogenic effect

FIGURE 83

EFFECT OF HUMAN PLASMA IgM ON GH 3 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

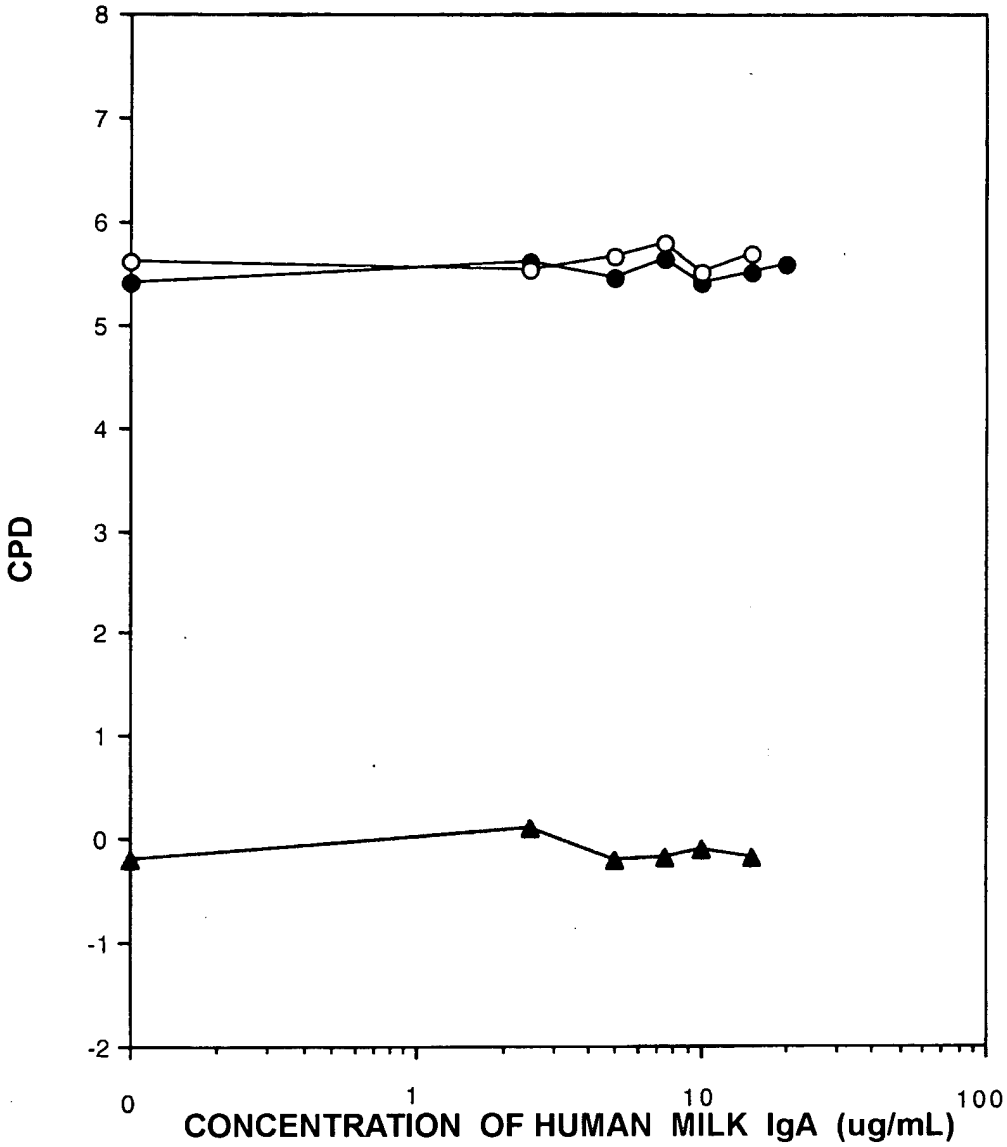
● = + E_2

■ = − E_2

▼ = Estrogenic effect

FIGURE 84

EFFECT OF HUMAN MILK SECRETORY IgA ON GH_3 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

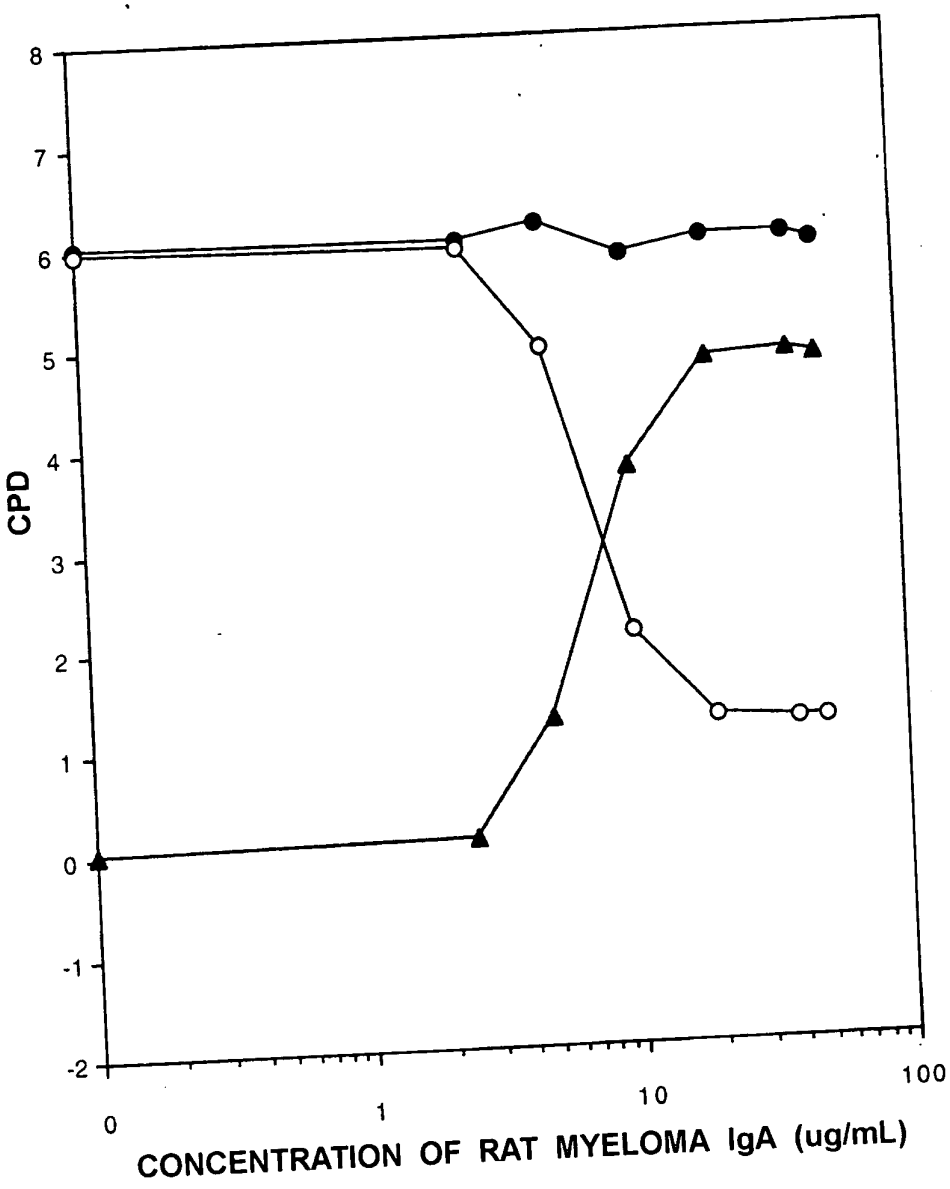
Closed circles = + E_2

Open circles = − E_2

Closed triangles = Estrogenic effect

FIGURE 85

EFFECT OF RAT MYELOMA IgA ON GH_4 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

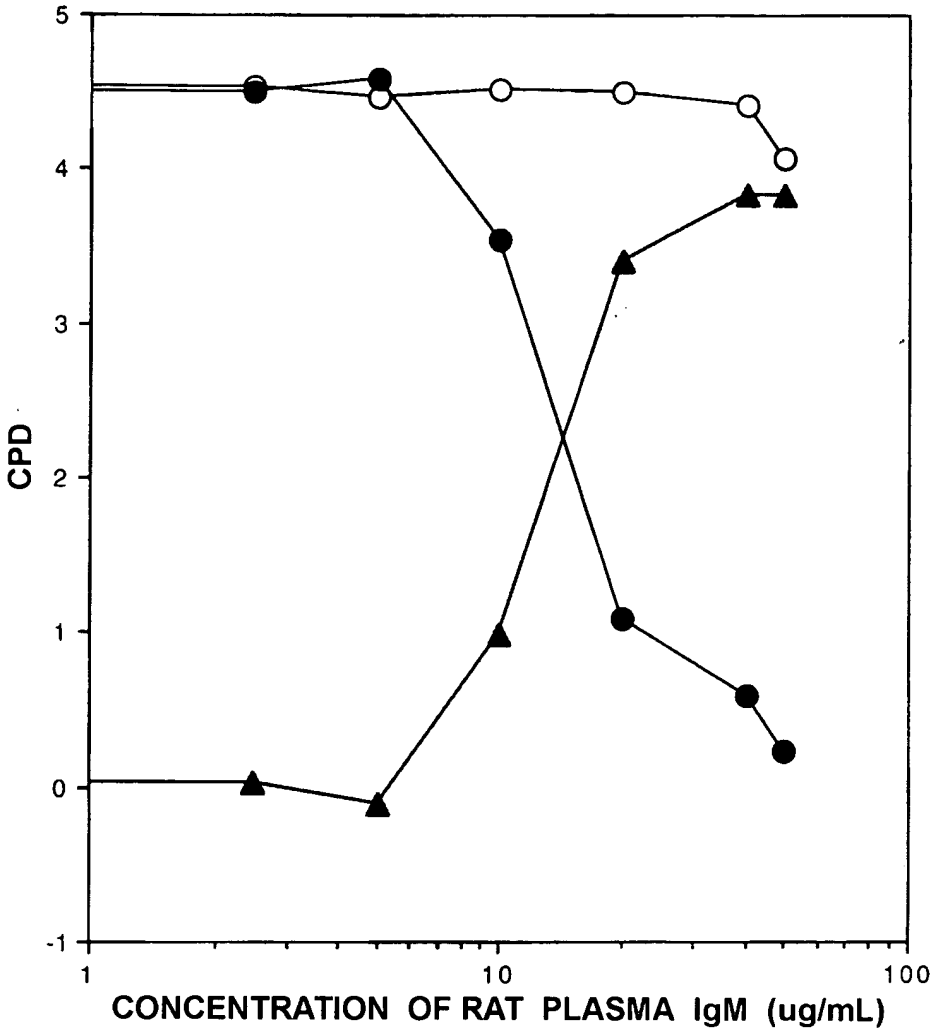
Closed circles = + E_2

Open circles = − E_2

Closed triangles = Estrogenic effect

FIGURE 86

EFFECT OF RAT PLASMA IgM ON GH_4 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

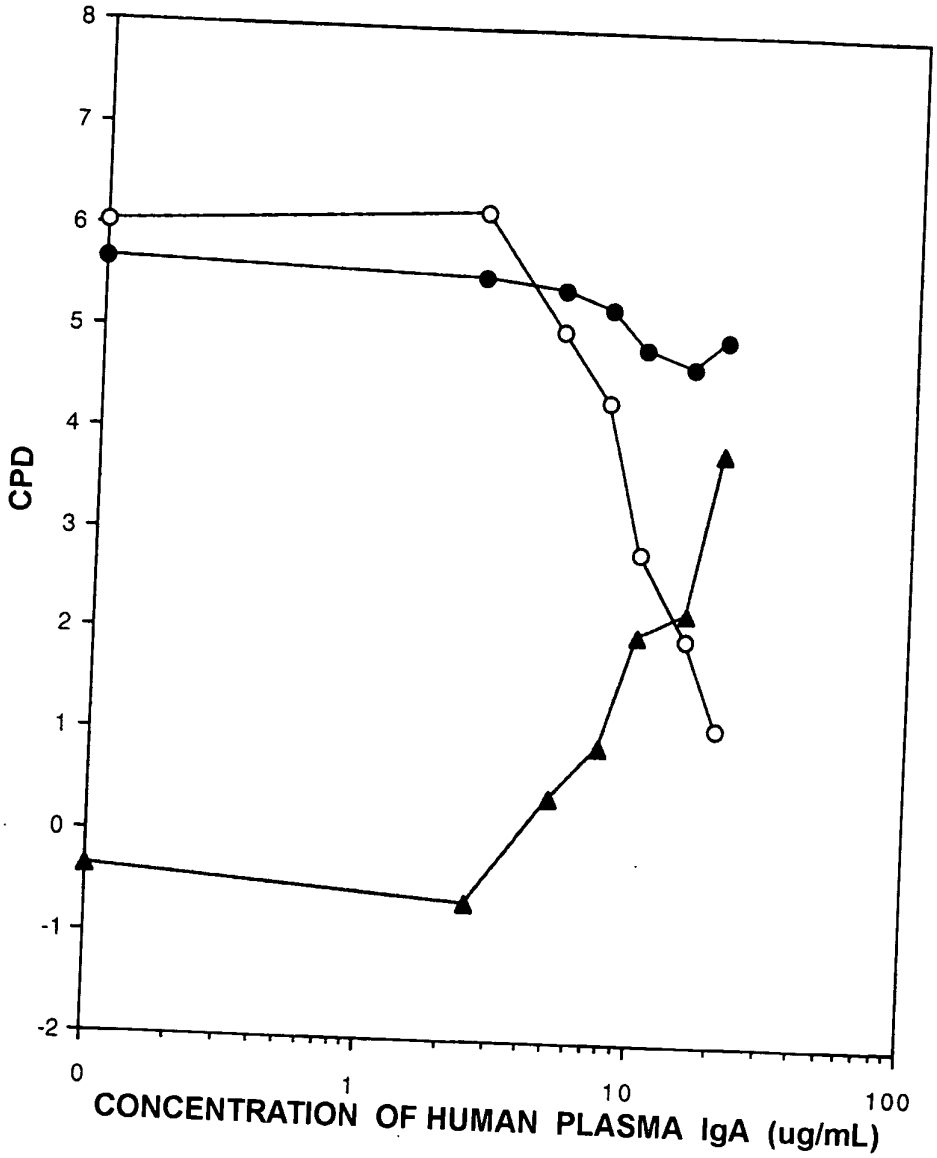
—○— = + E_2

—●— = − E_2

—▲— = Estrogenic effect

FIGURE 87

EFFECT OF HUMAN PLASMA IgA ON GH_4C_1 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

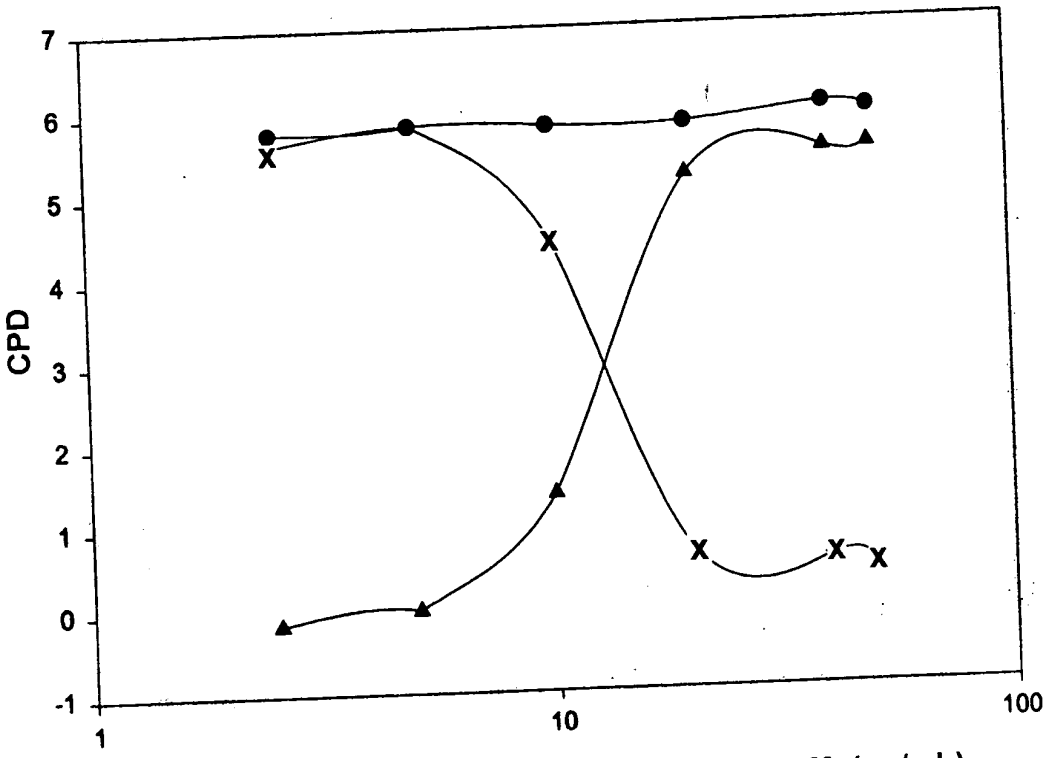
Closed circles = + E_2

Open circles = – E_2

Closed triangles = Estrogenic effect

FIGURE 88

EFFECT OF HUMAN PLASMA IgM ON GH_4C_1 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

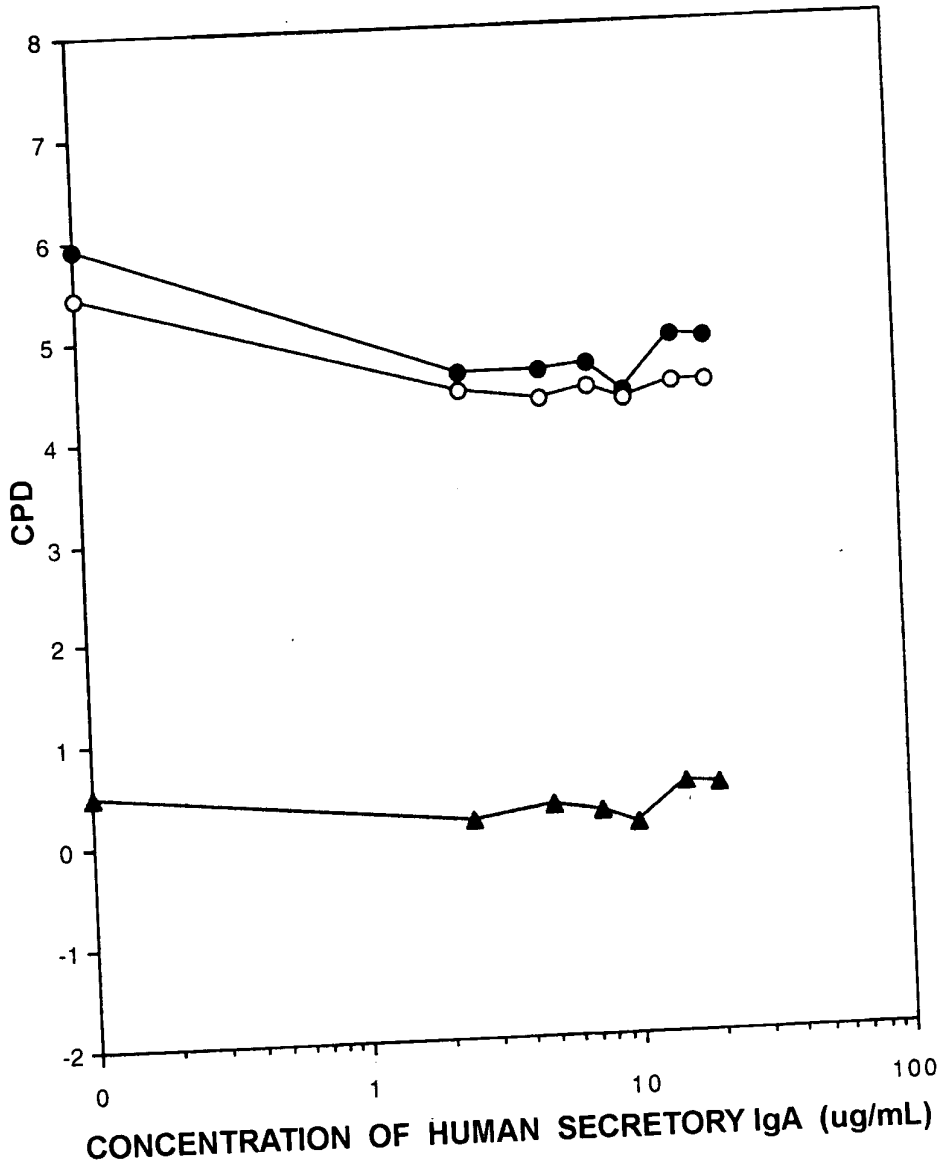
—●— = + E_2

—X— = − E_2

—▲— = Estrogenic effect

FIGURE 89

EFFECT OF HUMAN MILK SECRETORY IgA ON GH_4C_1 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

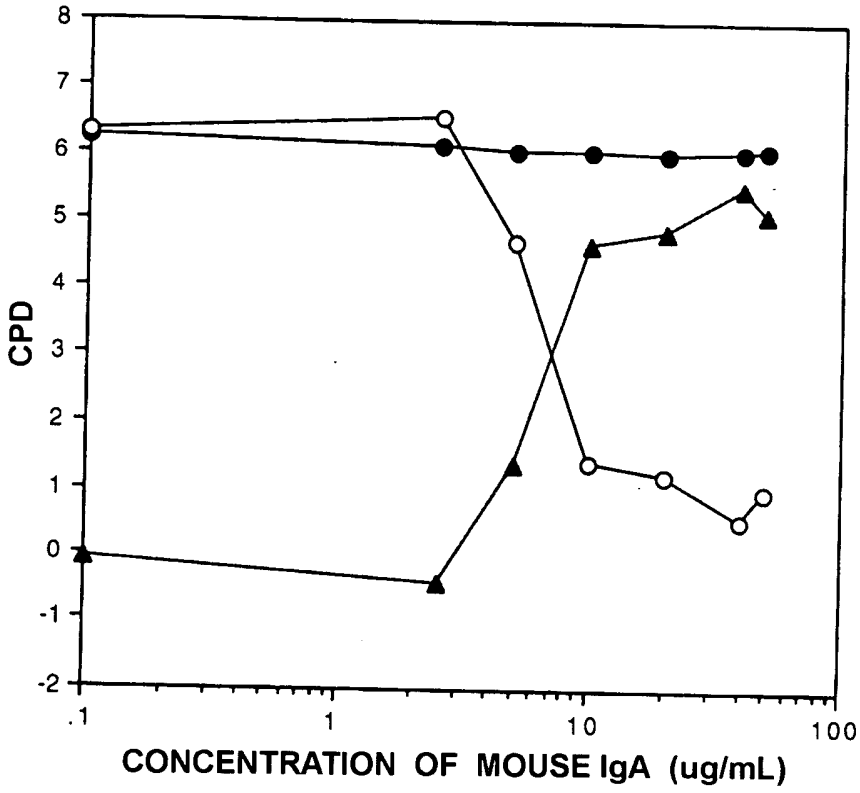
Closed circles = + E_2

Open circles = − E_2

Closed triangles = Estrogenic effect

FIGURE 90

EFFECT OF MOUSE IgA ON H301 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

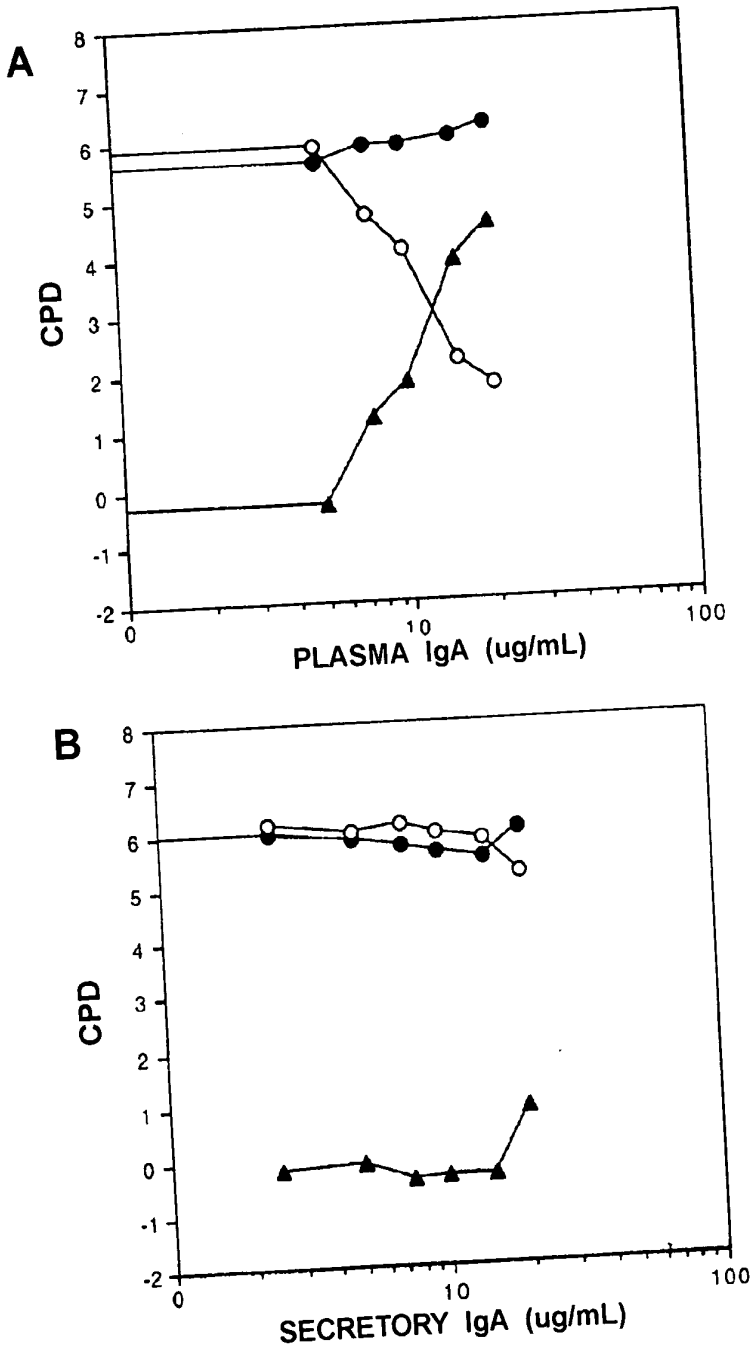
Closed circles = + E_2

Open circles = − E_2

Closed triangles = Estrogenic effect

FIGURE 91

EFFECT OF HUMAN PLASMA IgA (A) AND SECRETORY IgA (B) ON H301CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND: Clos d circles = + E_2

Open circles = − E_2

Closed triangles = Estrogenic effect

FIGURE 92

EFFECT OF ESTRADIOL ON H301 CELL GROWTH IN SERUM-FREE MEDIUM AND 40 ug/mL OF HUMAN IgM

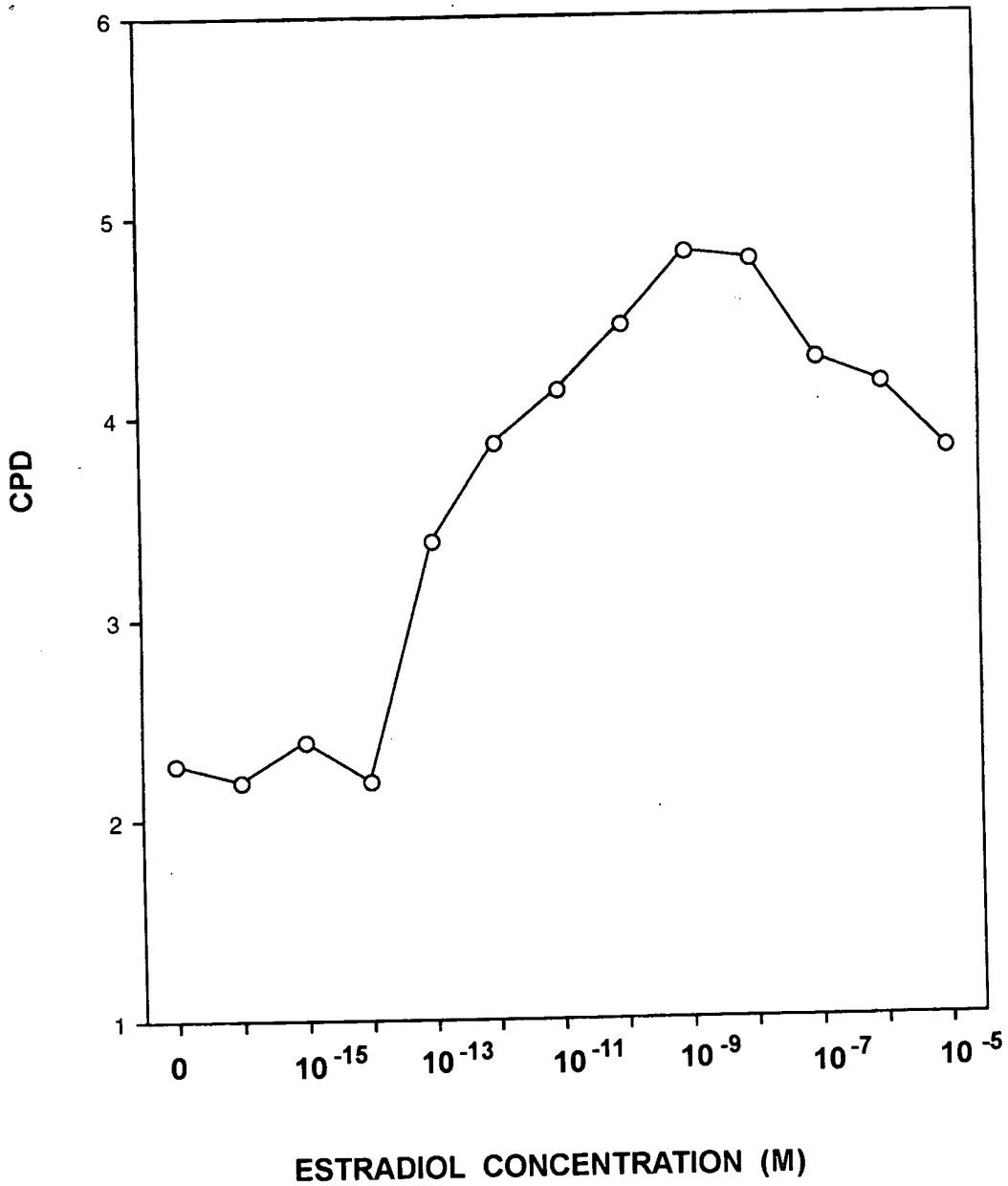
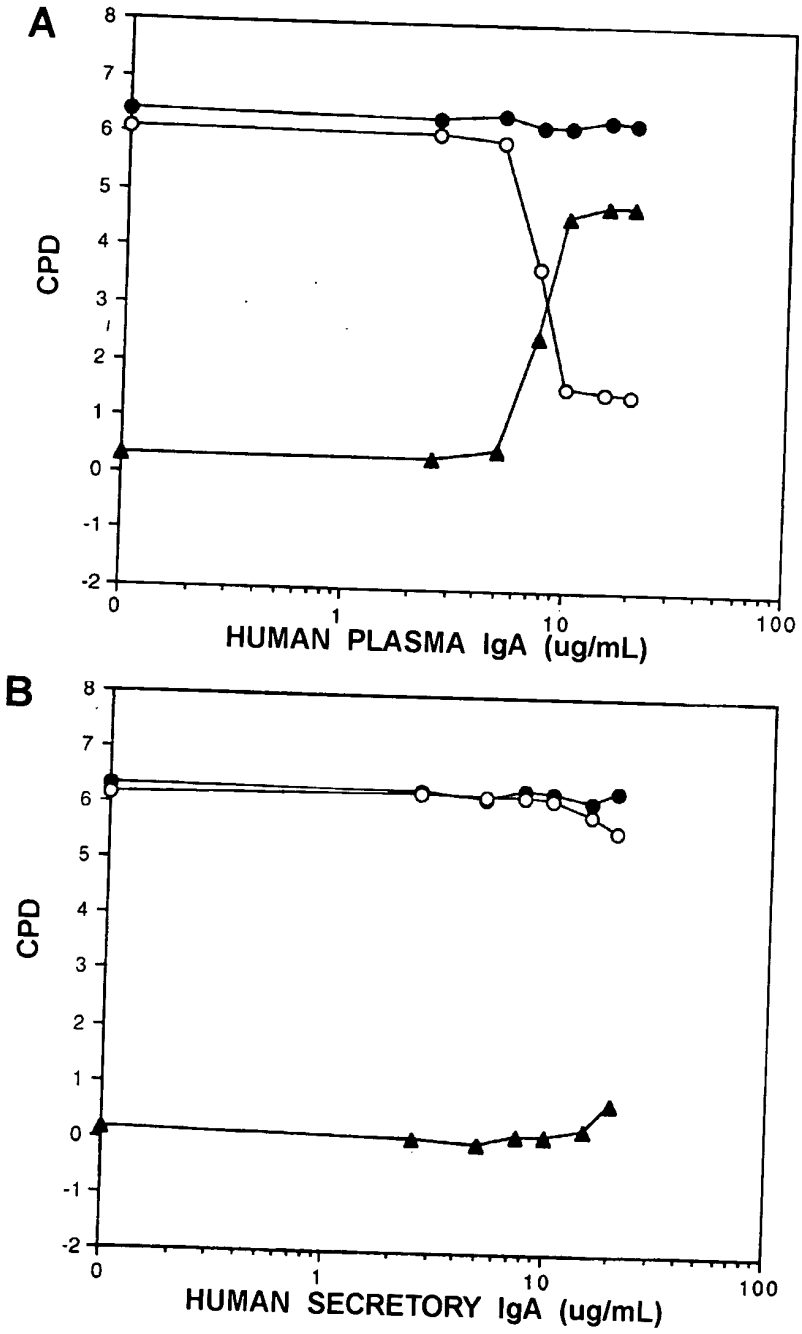


FIGURE 93

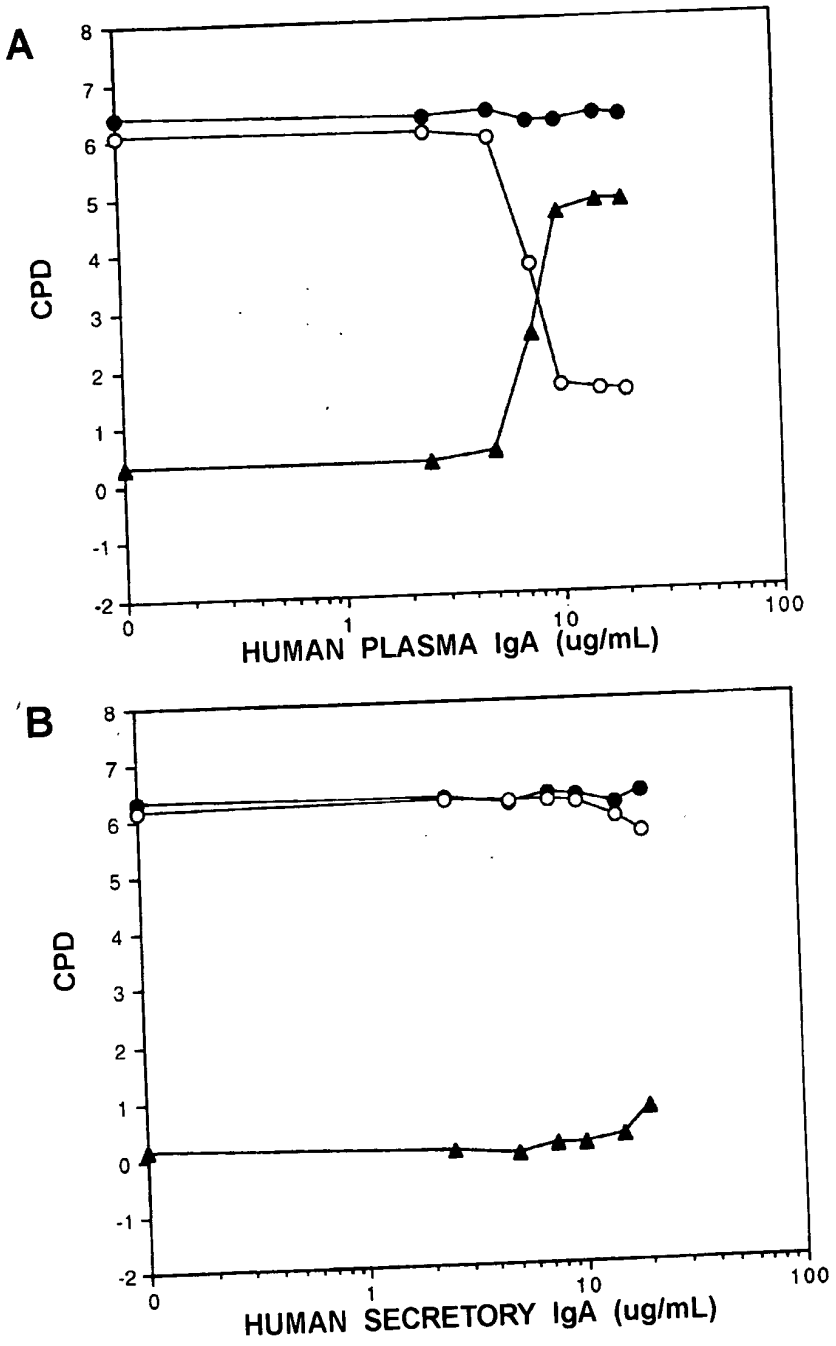
EFFECT OF HUMAN PLASMA IgA (A) AND SECRETORY IgA (B) ON MCF-7K CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND: Closed circles = + E_2
Open circles = − E_2
Closed triangles = Estrogenic effect

FIGURE 94

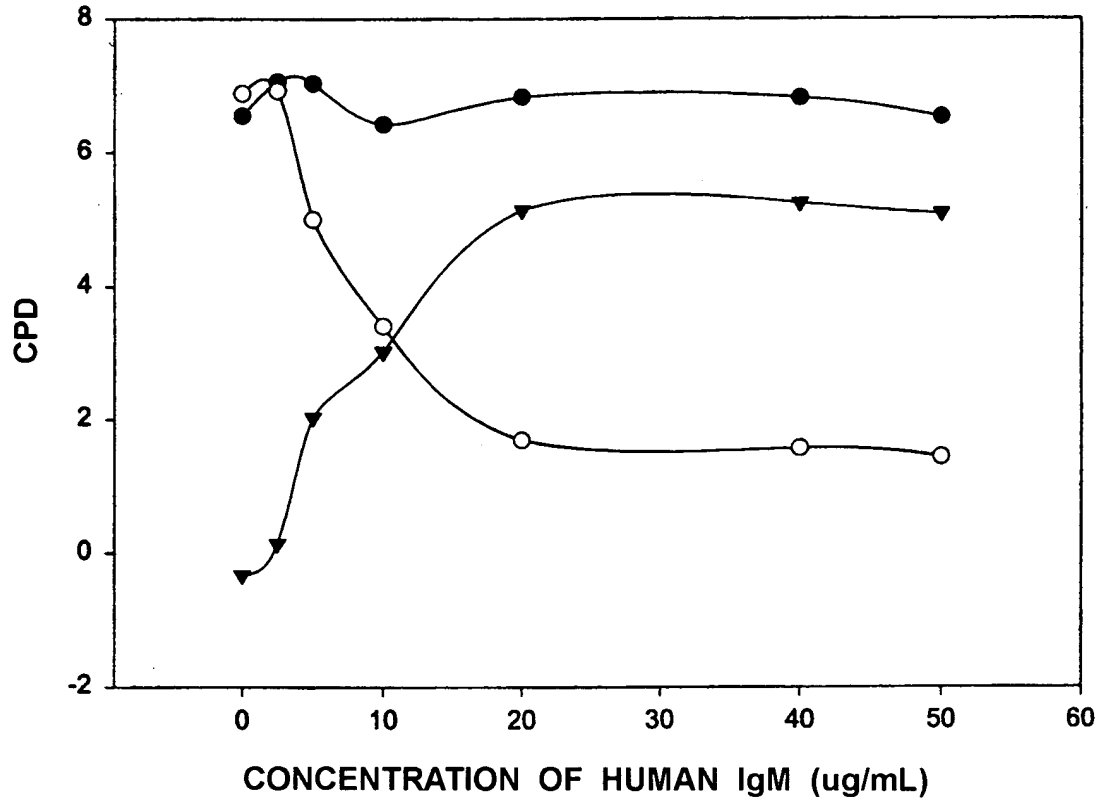
EFFECT OF HUMAN PLASMA IgA (A) AND SECRETORY IgA (B) ON MCF-7K CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND: Closed circles = + E_2
Open circles = − E_2
Closed triangles = Estrogenic effect

FIGURE 95

EFFECT OF HUMAN IgM ON MCF-7A CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

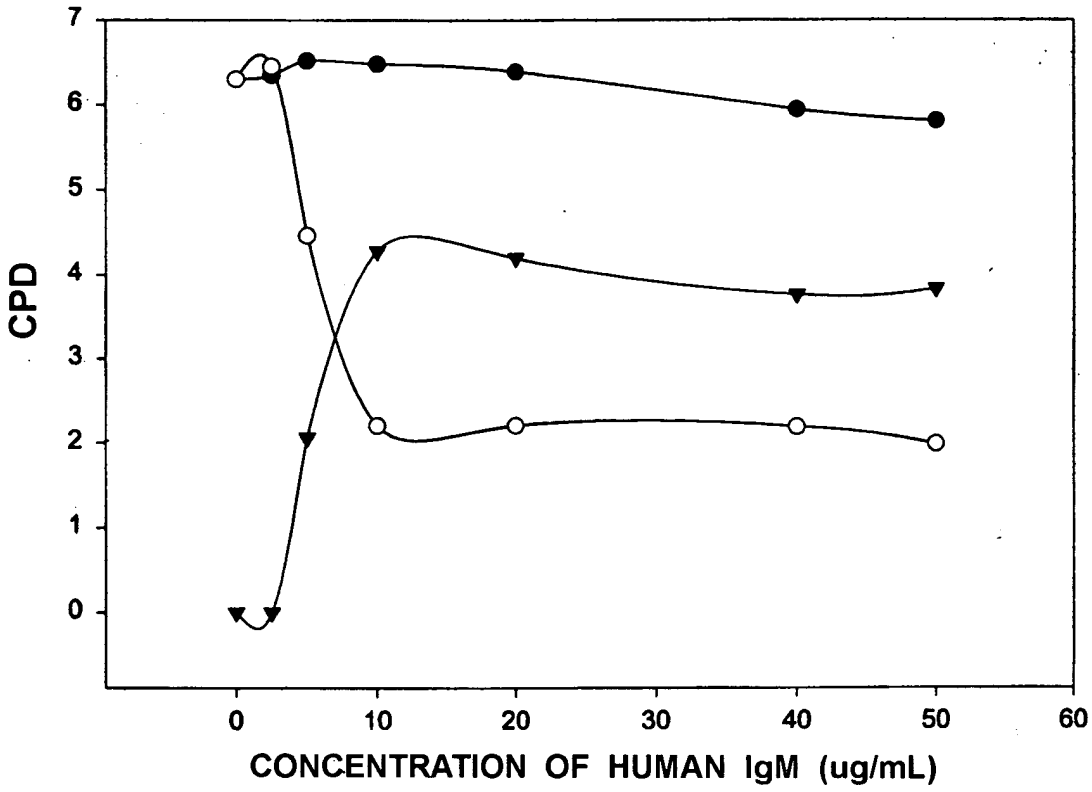
● = + E_2

○ = − E_2

▼ = Estrogenic effect

FIGURE 96

EFFECT OF HUMAN IgM ON MCF-7K CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND:

● = + E_2

○ = − E_2

▼ = Estrogenic effect

FIGURE 97

EFFECT OF ESTRADIOL ON MCF-7K CELL GROWTH IN SERUM-FREE MEDIUM WITH 40 ug/mL HUMAN IgM

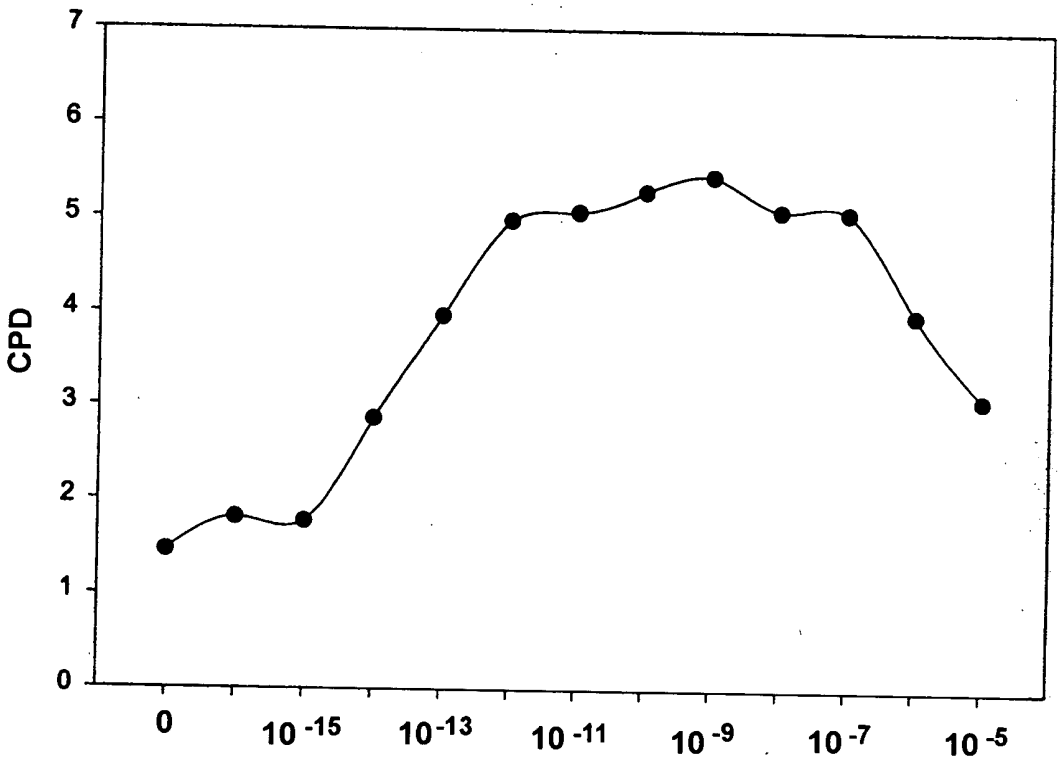
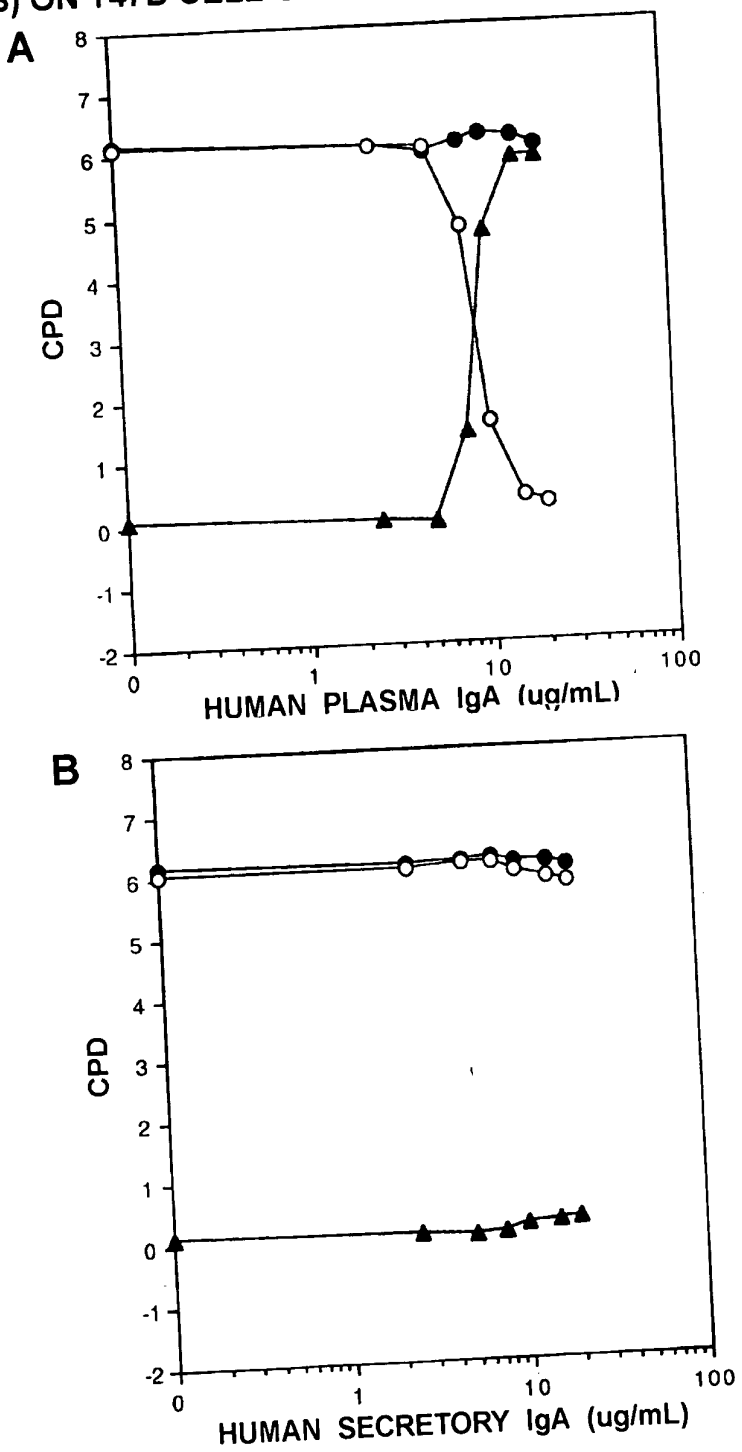


FIGURE 98

EFFECT OF HUMAN PLASMA IgA (A) AND SECRETORY IgA (B) ON T47D CELL GROWTH IN SERUM-FREE MEDIUM



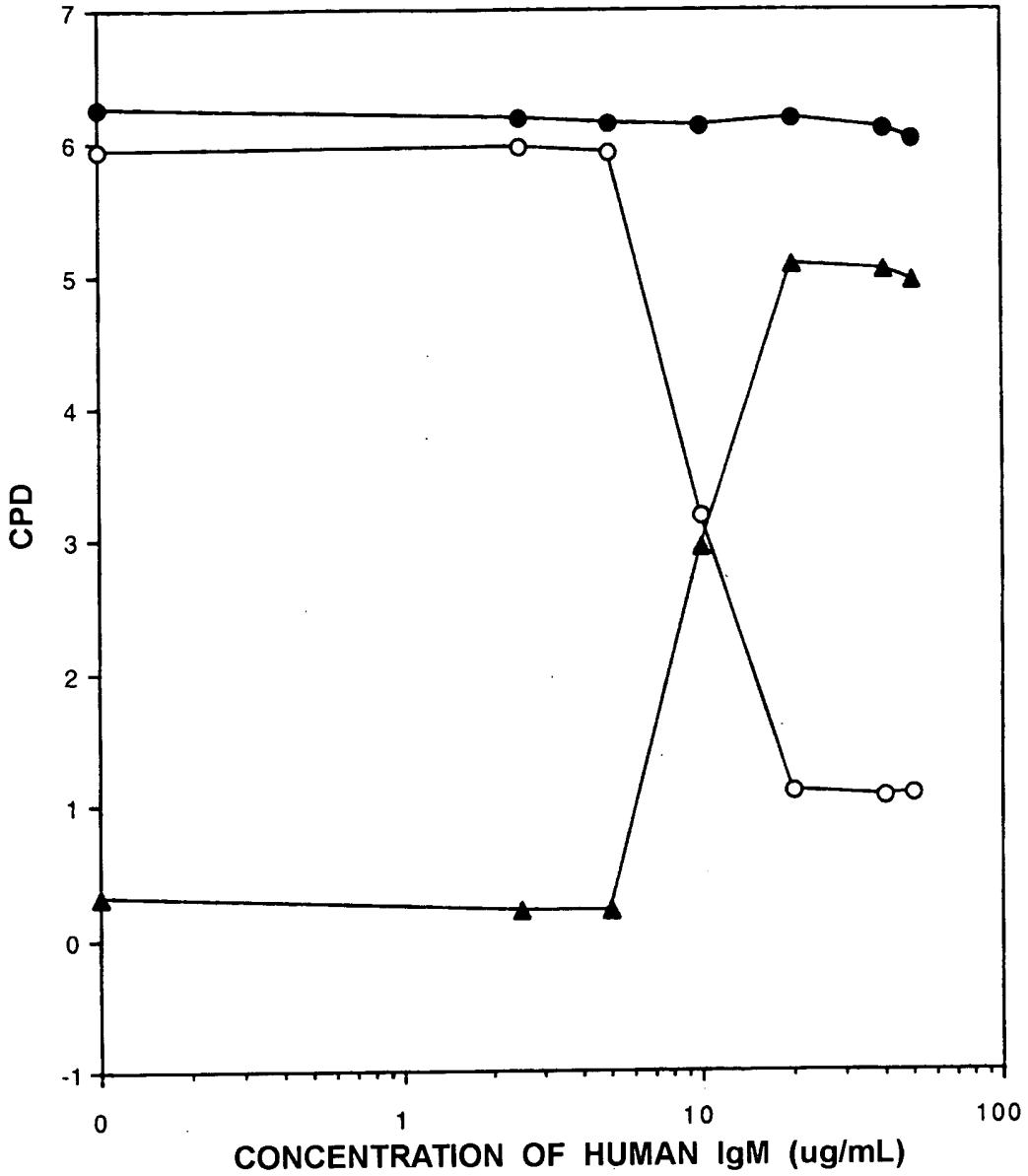
LEGEND: Closed circles = + E_2

Open circles = – E_2

Closed triangles = Estrogenic effect

FIGURE 99

EFFECT OF HUMAN IgM ON T47D CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND: Closed circles = + E_2

Open circles = − E_2

Closed triangles = Estrogenic effect

FIGURE 100

EFFECT OF ESTRADIOL ON T47D CELL GROWTH IN SERUM-FREE MEDIUM WITH 40 ug/mL HUMAN IgM

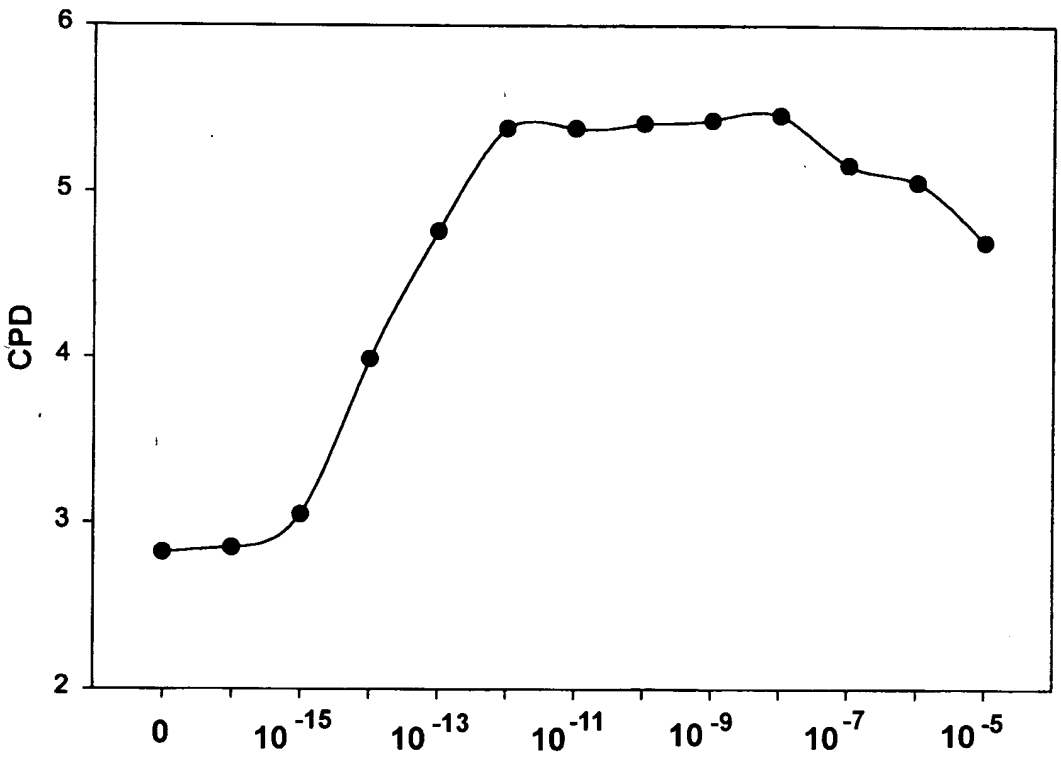
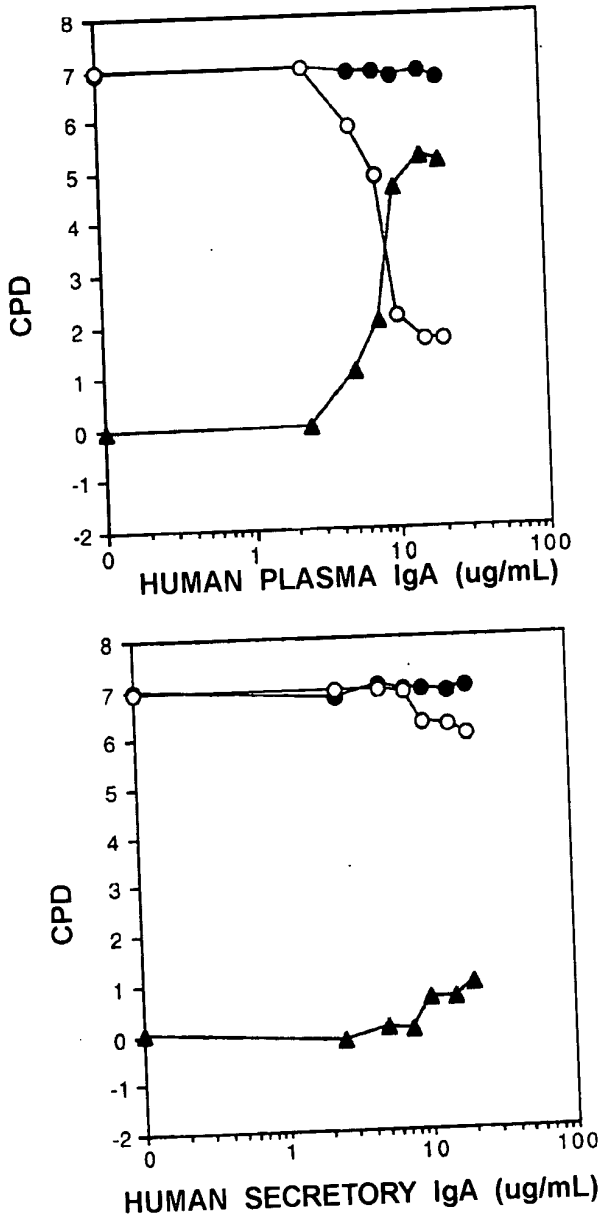


FIGURE 101

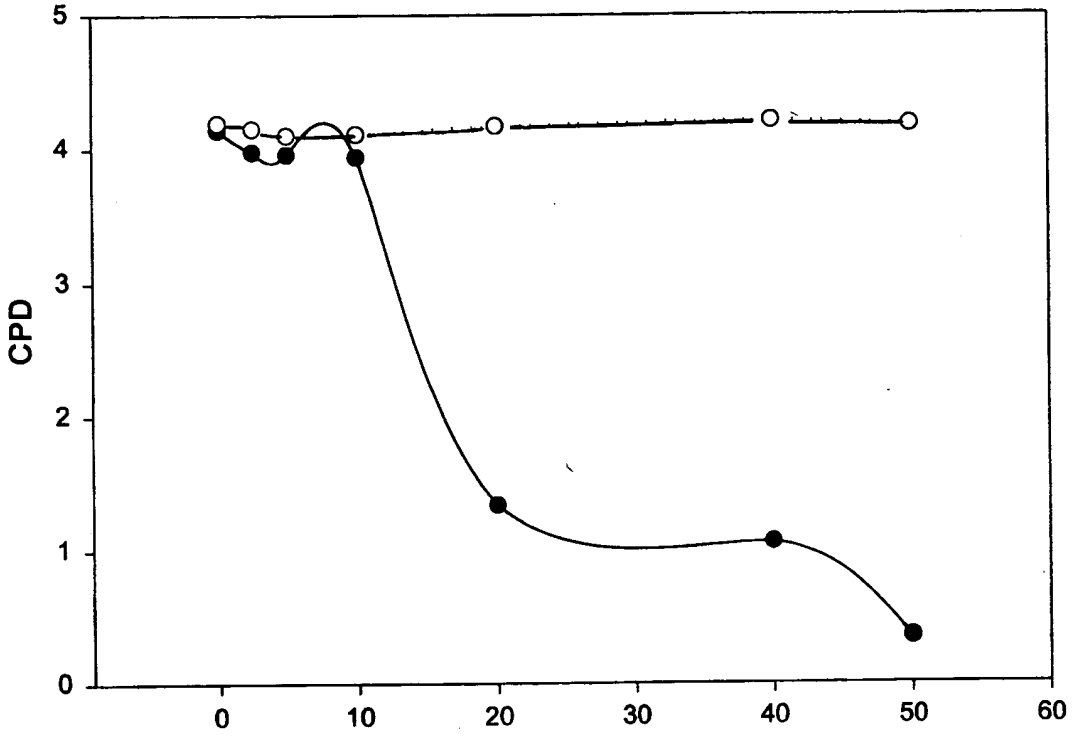
EFFECT OF HUMAN PLASMA IgA (A) AND SECRETORY IgA (B) ON ZR-75-1 CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND: Closed circles = + E_2
Open circles = − E_2
Closed triangles = Estrogenic effect

FIGURE 102

EFFECT OF HUMAN PLASMA IgM ON ZR-75-1 CELL GROWTH IN SERUM-FREE MEDIUM



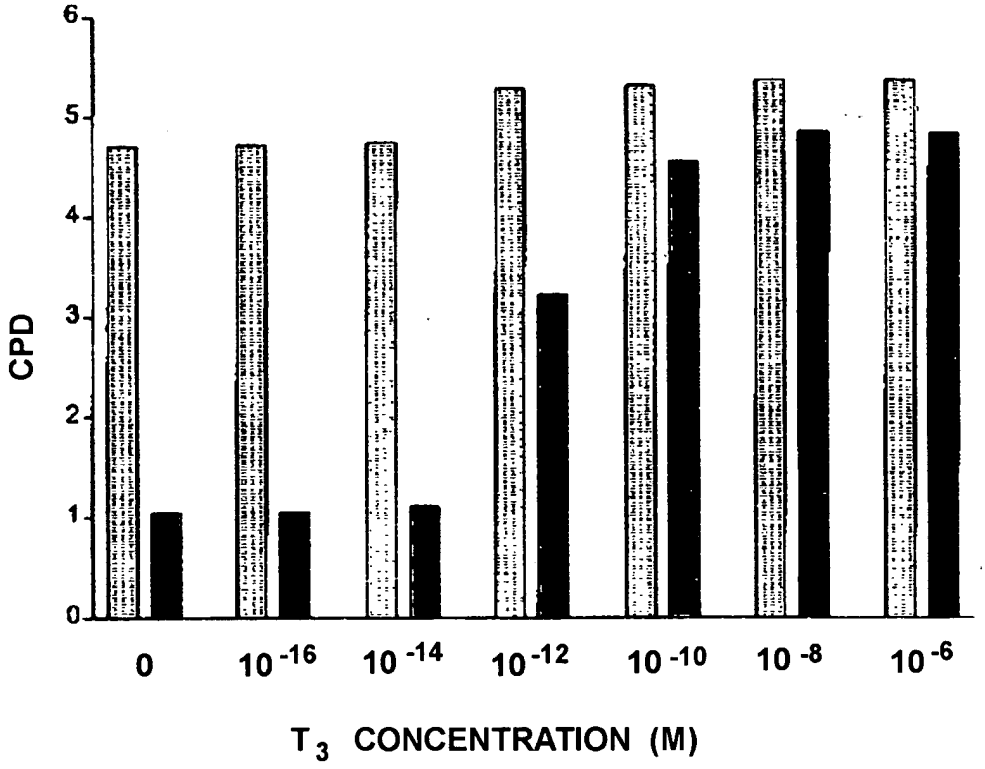
LEGEND:

—●— = – E_2

–○– = + E_2

FIGURE 103

EFFECT OF HUMAN IgM ON HT-29 CELL GROWTH IN THE PRESENCE OF INCREASING CONCENTRATIONS OF T_3



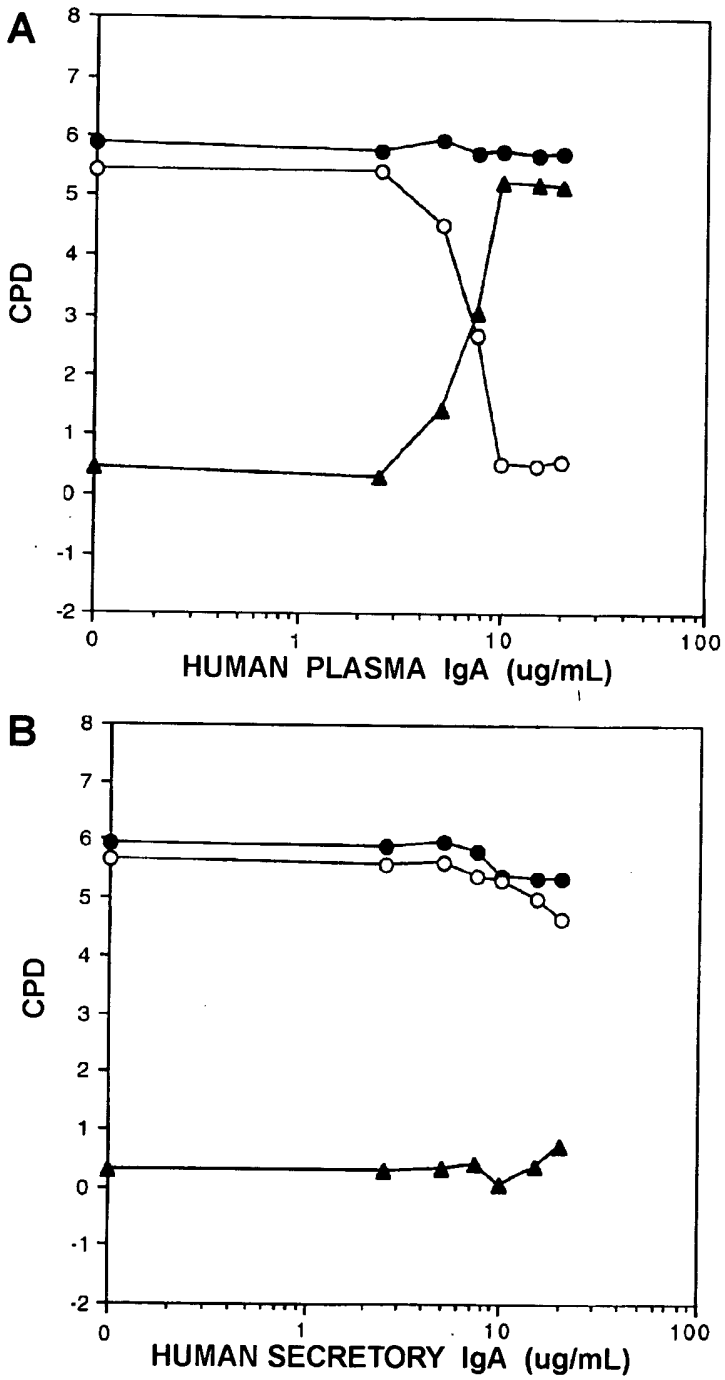
LEGEND:

= T_3 Titration

= T_3 Titration + 40 ug/mL IgM

FIGURE 104

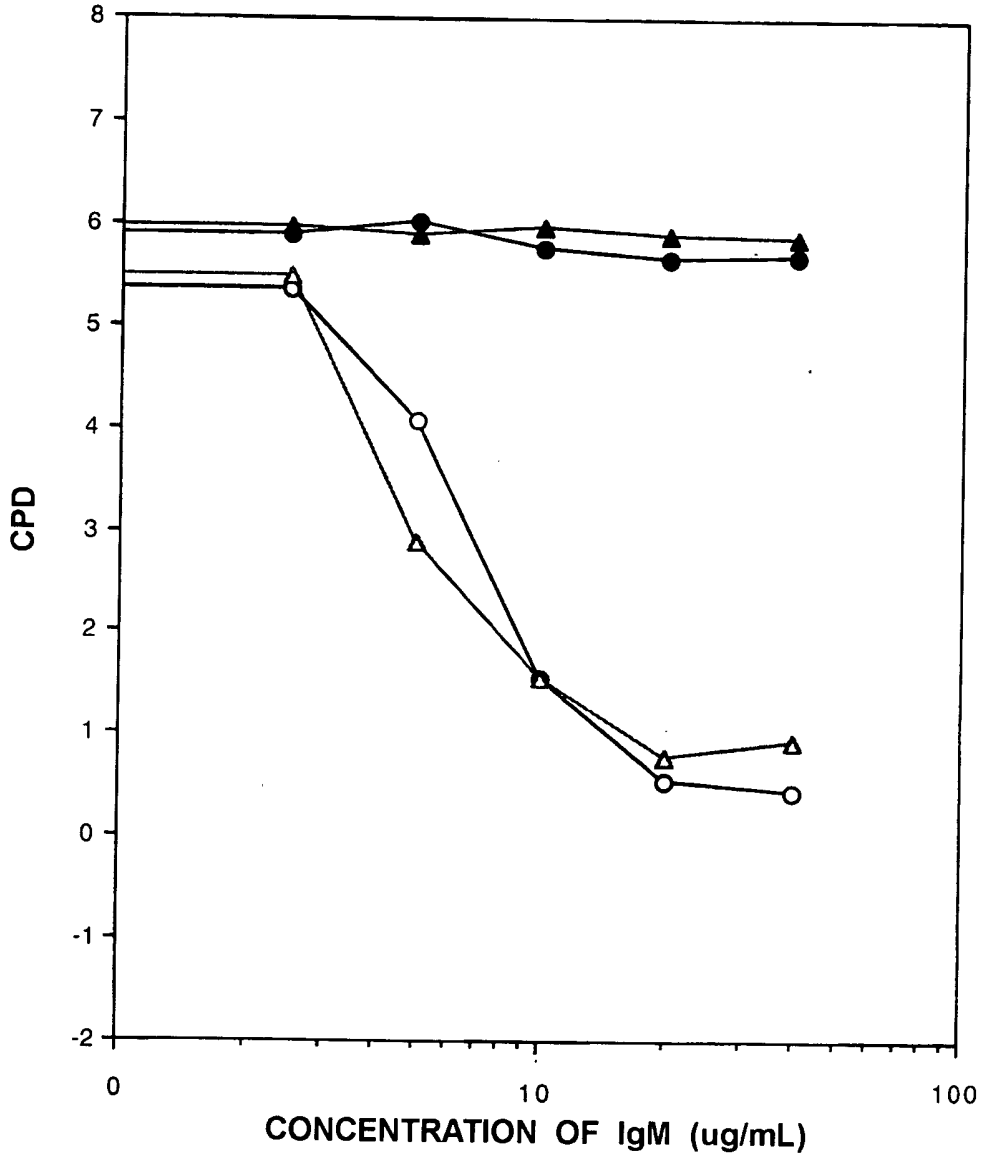
EFFECT OF HUMAN PLASMA IgA (A) AND SECRETORY IgA (B) ON LNCaP CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND: Closed circl s = + E_2
Open circles = − E_2
Closed triangles = Estrogenic effect

FIGURE 105

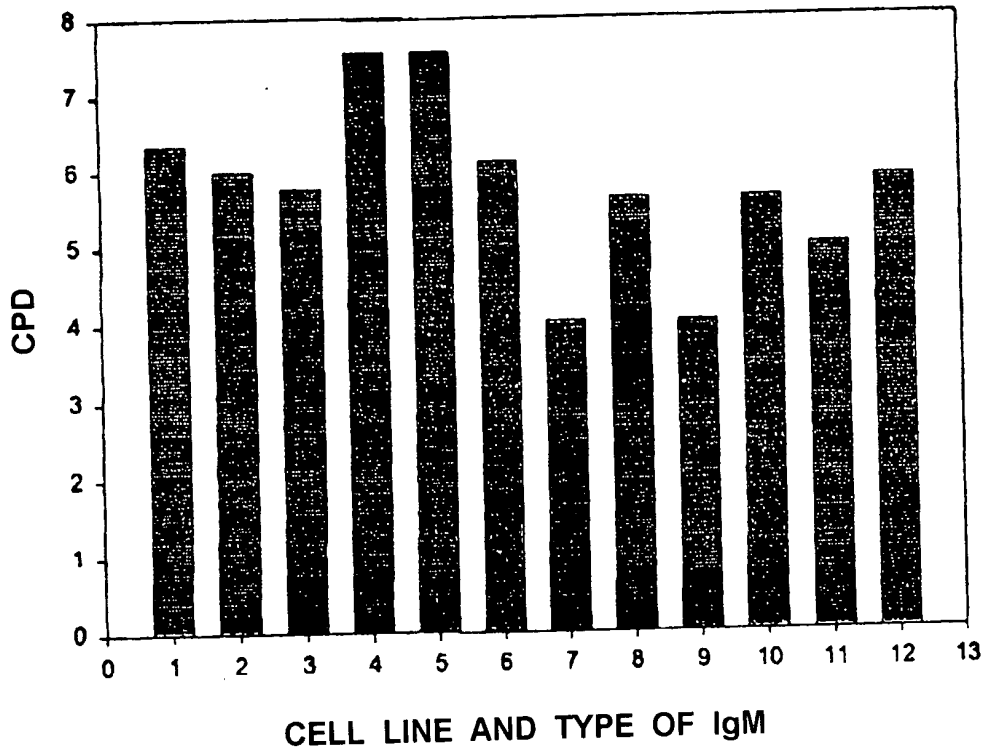
EFFECTS OF HUMAN PLASMA IgM VS IgM DERIVED FROM MYELOMA CELLS ON LNCaP CELL GROWTH IN SERUM-FREE MEDIUM WITH AND WITHOUT DHT



LEGEND:
- = DHT + Myeloma IgM
- = Myeloma IgM only
- = DHT + Plasma IgM
- = Plasma IgM only

FIGURE 106

ESTROGENIC EFFECT OF 50 ug/mL OF VARIOUS IgM'S ON SEVERAL DIFFERENT CELL LINES

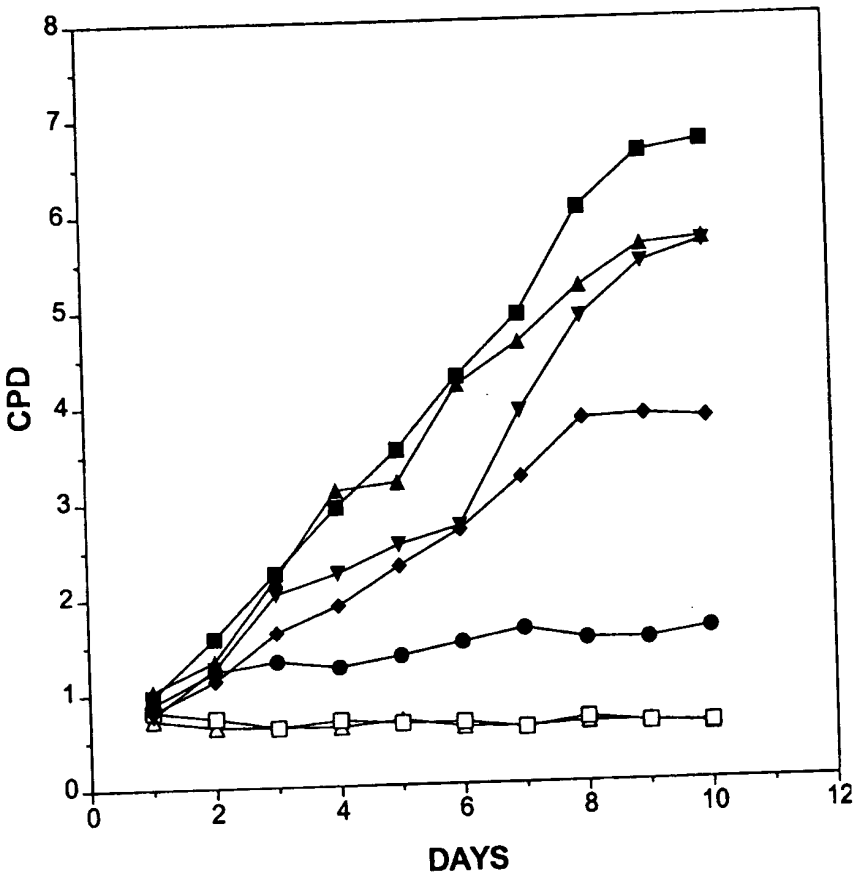


LEGEND:

1. Human IgM on MTW9/PL2 Cells = 6.36 cpd
2. Mouse IgM on MTW9/PL2 Cells = 6.00 cpd
3. Rat IgM on MTW9/PL2 Cells = 5.77 cpd
4. Human IgM on H301 Cells = 7.57 cpd
5. Mouse IgM on H301 Cells = 7.56 cpd
6. Rat IgM on H301 Cells = 6.11 cpd
7. Human IgM on GH1 Cells = 4.12 cpd
8. Rat IgM on GH1 Cells = 5.83 cpd
9. Human IgM on GH3 Cells = 4.09 cpd
10. Human IgM on GH4 Cells = 5.41 cpd
11. Human IgM on MCF-7A Cells = 5.01 cpd
12. Human IgM on MCF-7K C lls = 5.89 cpd

FIGURE 107

EFFECT OF TAMOXIFEN ON T47D CELL GROWTH IN DDM-2MF DEFINED MEDIUM

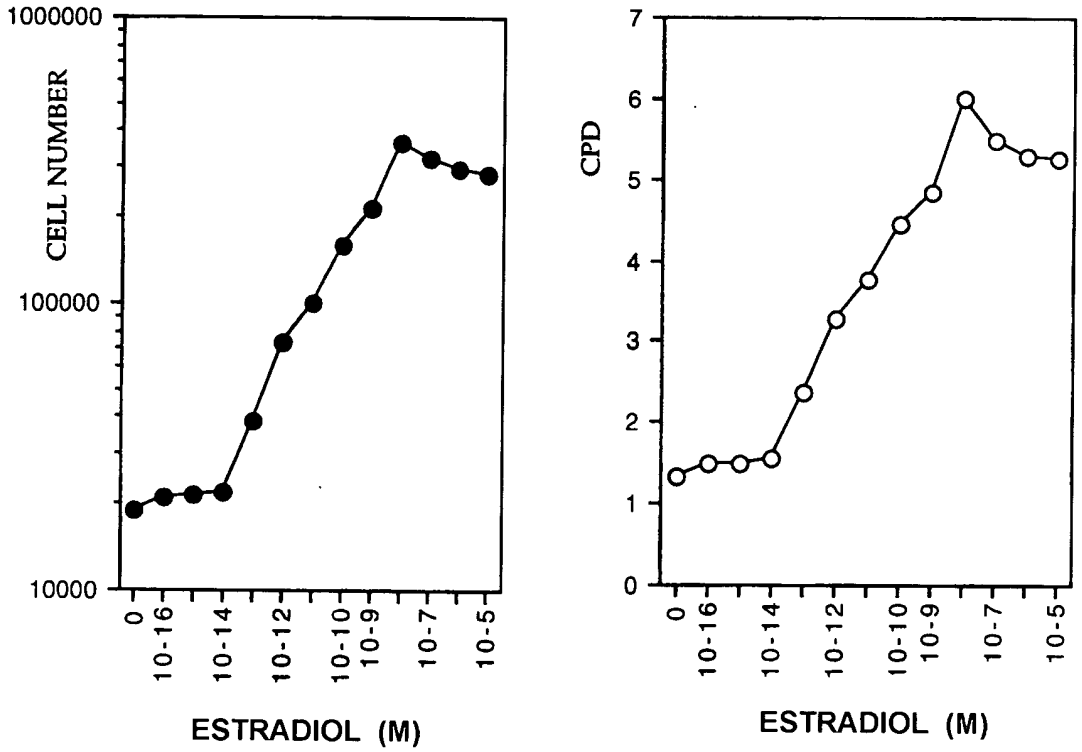


LEGEND:

- SFM + E_2
- SFM - E_2
- SFM + 10^{-9} M TAM
- SFM + 10^{-8} M TAM
- SFM + 10^{-7} M TAM
- SFM + 10^{-6} M TAM
- SFM + 10^{-5} M TAM

FIGURE 108

EFFECT OF INCREASING ESTRADIOL CONCENTRATIONS ON T47D CELL GROWTH IN SERUM-FREE AND PHENOL- RED FREE MEDIUM WITH 10^{-7} TAMOXIFEN

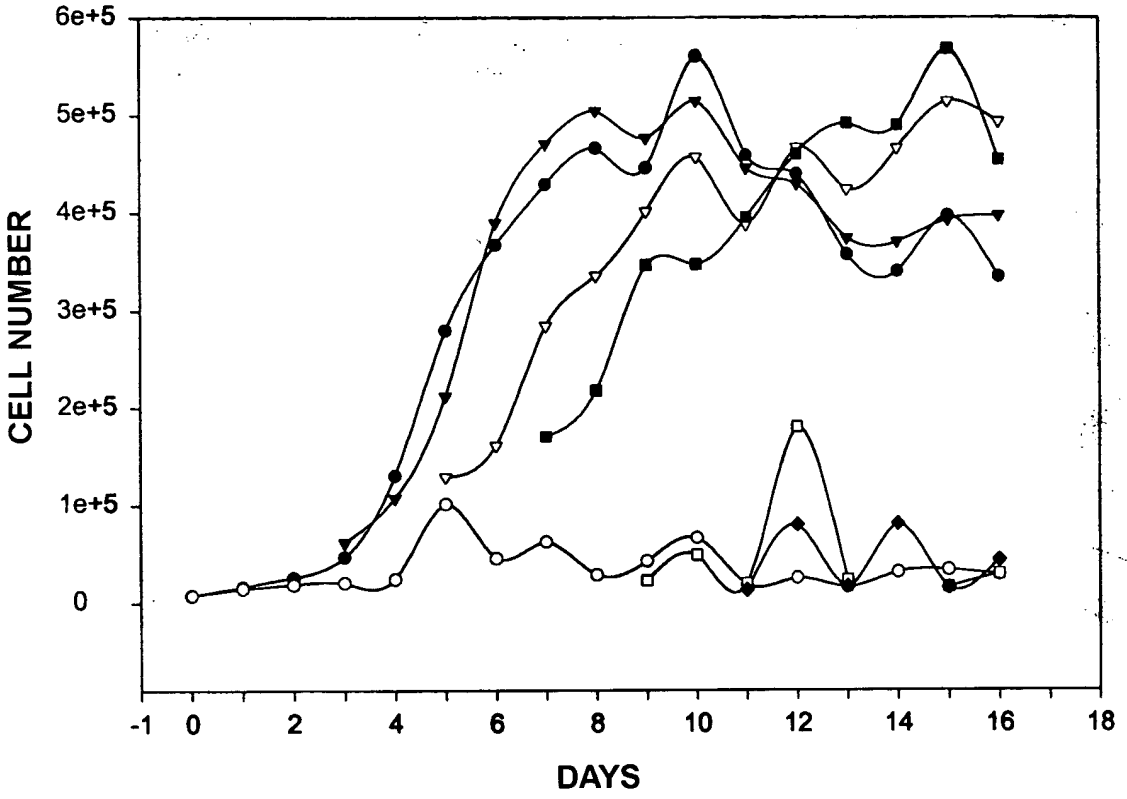


NOTE:

DATA ARE EXPRESSED AS BOTH CELL NUMBER AND CPD

FIGURE 109

E_2 RESCUE OF MTW9/PL2 CELL GROWTH IN SERUM-FREE MEDIUM WITH 40 ug/mL HORSE IgM



LEGEND:
- = E_2 Added on Day 0
- = No E_2
- = E_2 Added on Day 2
- = E_2 Added on Day 4
- = E_2 Added on Day 6
- = E_2 Added on Day 8
- = E_2 Added on Day 10

FIGURE 110

SUMMARY OF E_2 RESCUE OF MTW9/PL2 CELL GROWTH IN SERUM-FREE MEDIUM WITH 40 ug/mL HORSE IgM

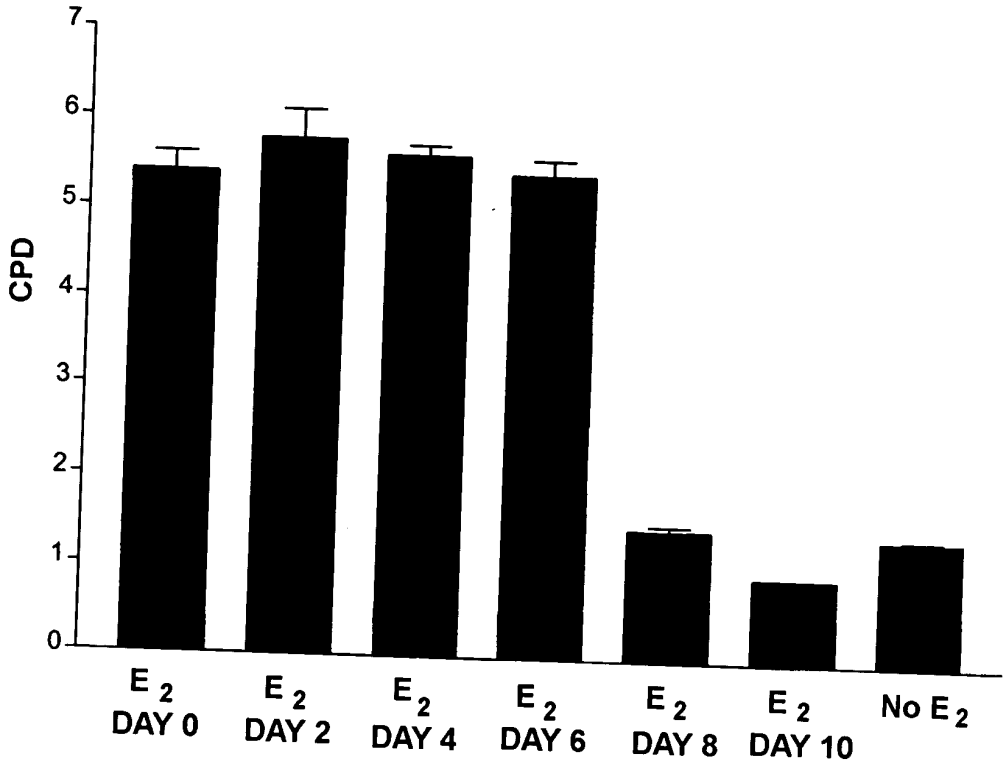
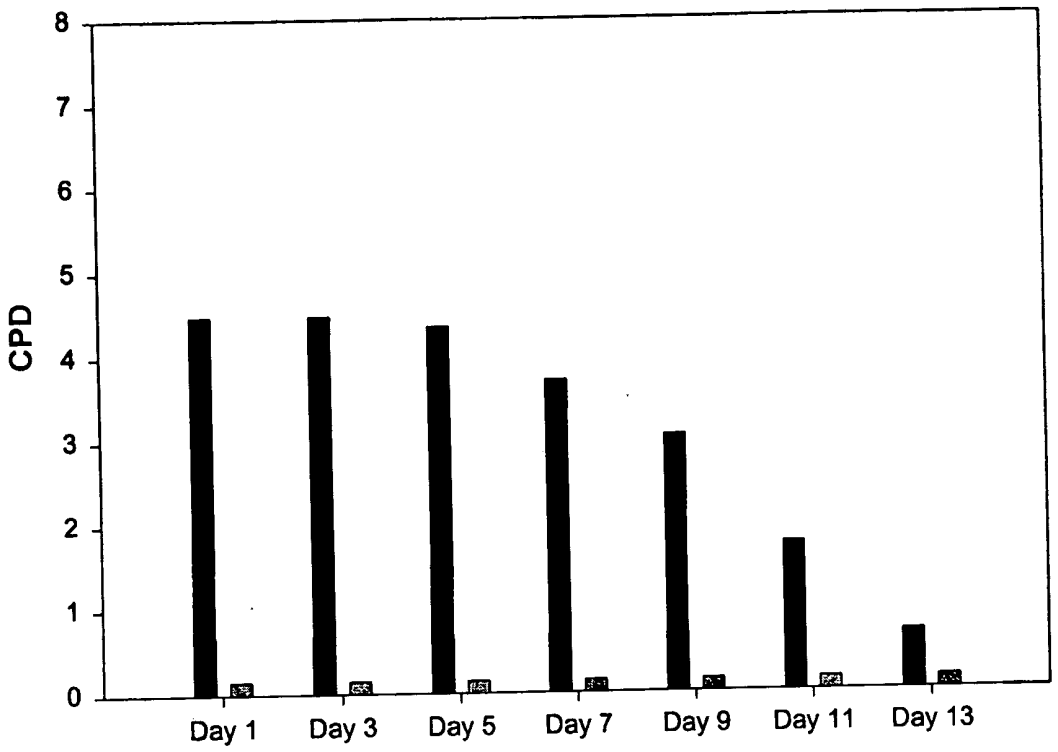


FIGURE 111

E_2 RESCUE OF T47D CELL GROWTH IN SERUM-FREE MEDIUM WITH 40 ug/mL HORSE IgM



E_2 ADDITION (DAY)

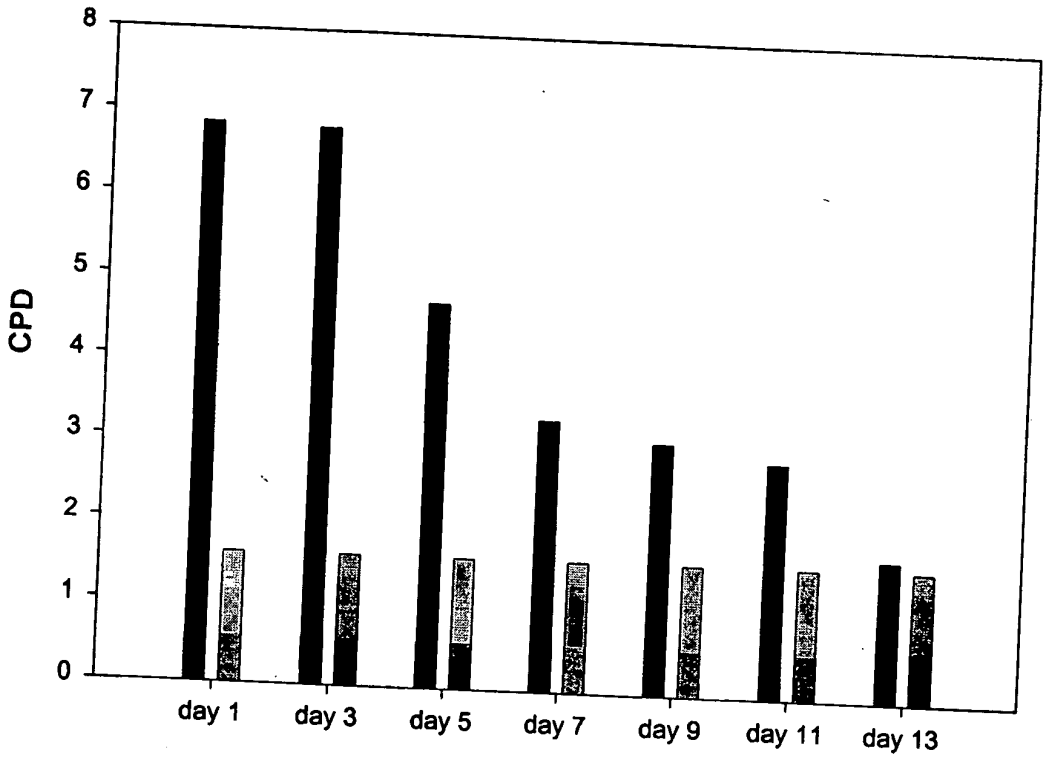
LEGEND:

= + E_2

= − E_2

FIGURE 112

ESTROGEN RESCUE OF MCF-7A CELL GROWTH IN SERUM-FREE MEDIUM WITH 40 ug/mL OF HUMAN SERUM IgM



E_2 ADDITION (DAY)

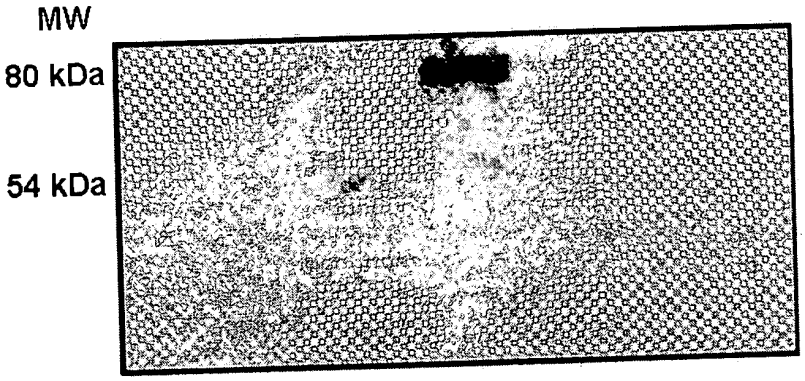
LEGEND:

= + E_2

= − E_2

FIGURE 113

DETECTION OF SECRETORY COMPONENT IN SECRETORY IgA WITH ANTI-SC ANTIBODY



20 ug/mL APPLIED IN ALL LINES

IgA = Human Plasma

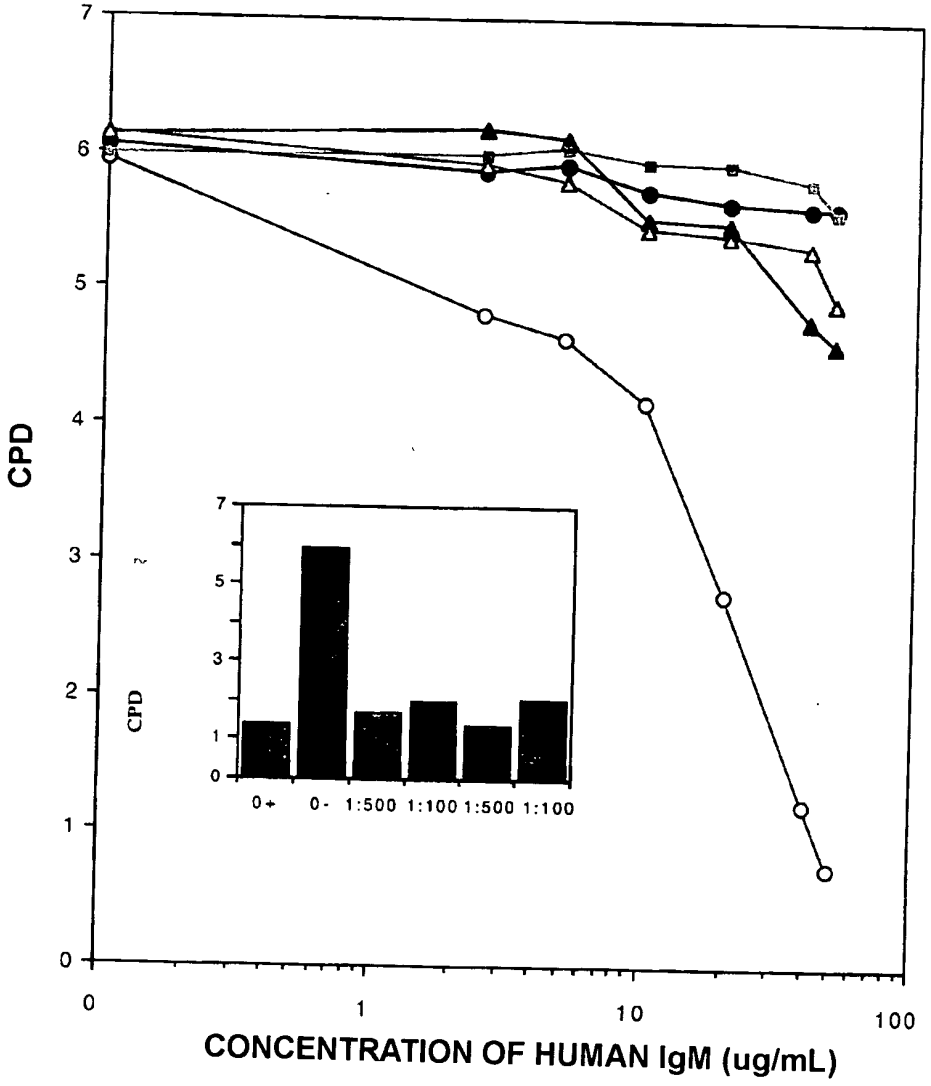
IgG = Human Plasma

Secretory IgA = IgA from Milk

Albumin = Human

FIGURE 114

HUMAN IgM TITRATION ON T47D CELLS GROWN IN SERUM-FREE MEDIUM WITH DIFFERENT DILUTIONS OF ANTI-SC ANTIBODY



LEGEND: —●— = + E_2

—○— = − E_2

—▲— = 1:5000 Dilution of Anti-SC Antibody

—△— = 1:1000 Dilution of Anti-SC Antibody

—■— = 1:500 Dilution of Anti-SC Antibody

INSERT: EFFECT OF RABBIT SERUM ON T47D CELLS INCUBATED WITH 40 ug/mL HUMAN IgM

FIGURE 115

EFFECT OF IgA ON LNCaP GROWTH IN THE PRESENCE OF ANTI-SECRETORY COMPONENT ANTIBODY AT DIFFERENT DILUTIONS

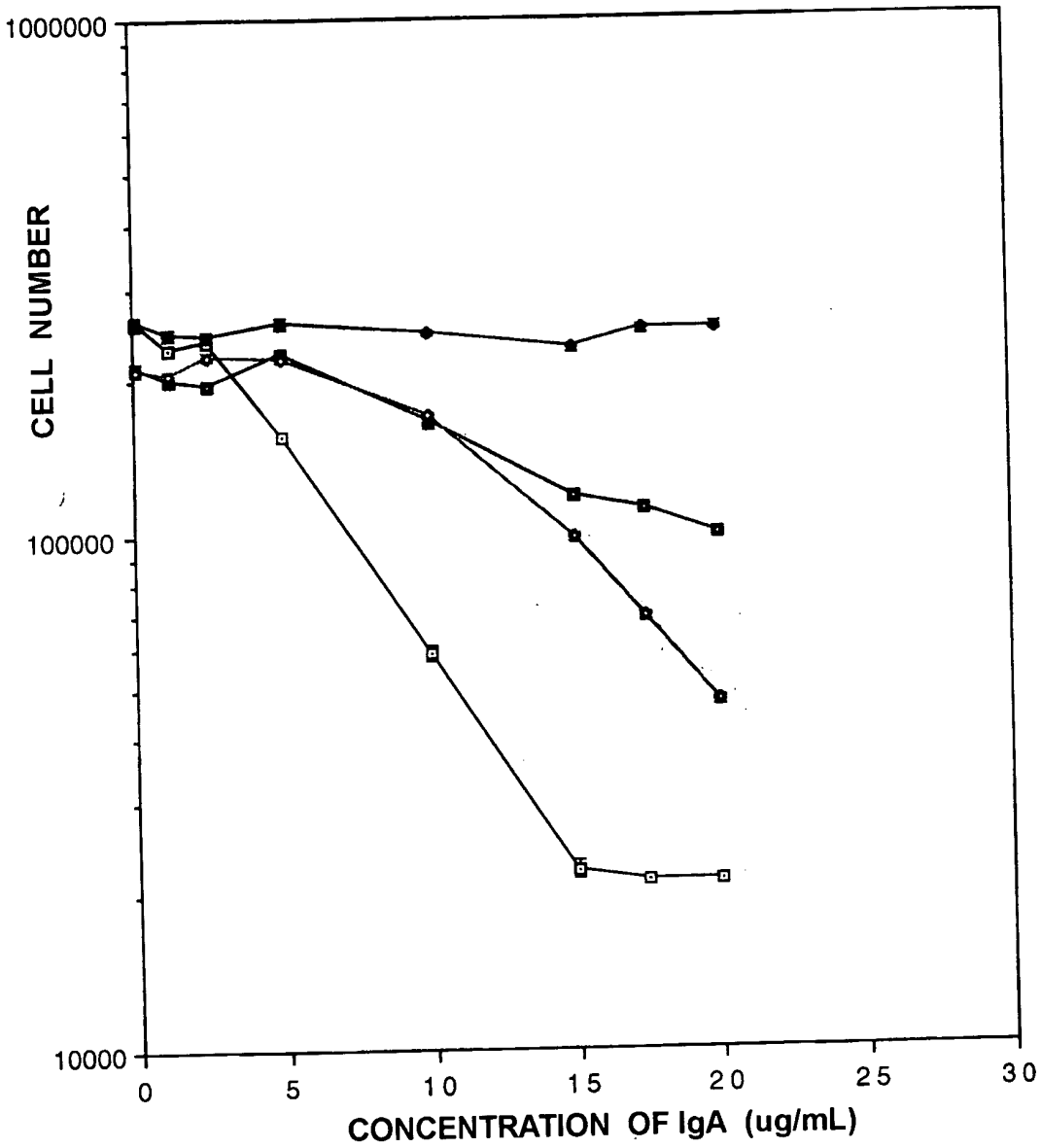
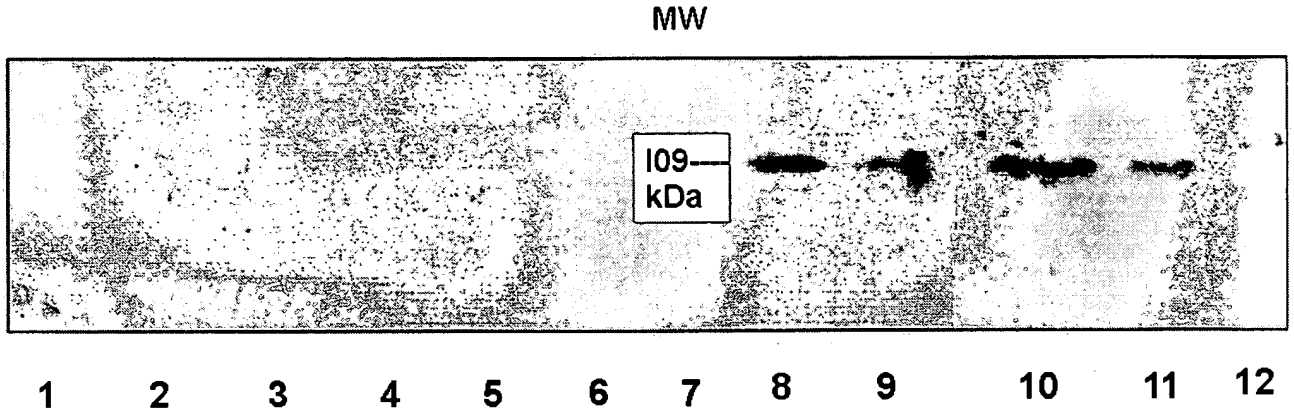


FIGURE 116

WESTERN BLOT: ANTI-SECRETORY COMPONENT

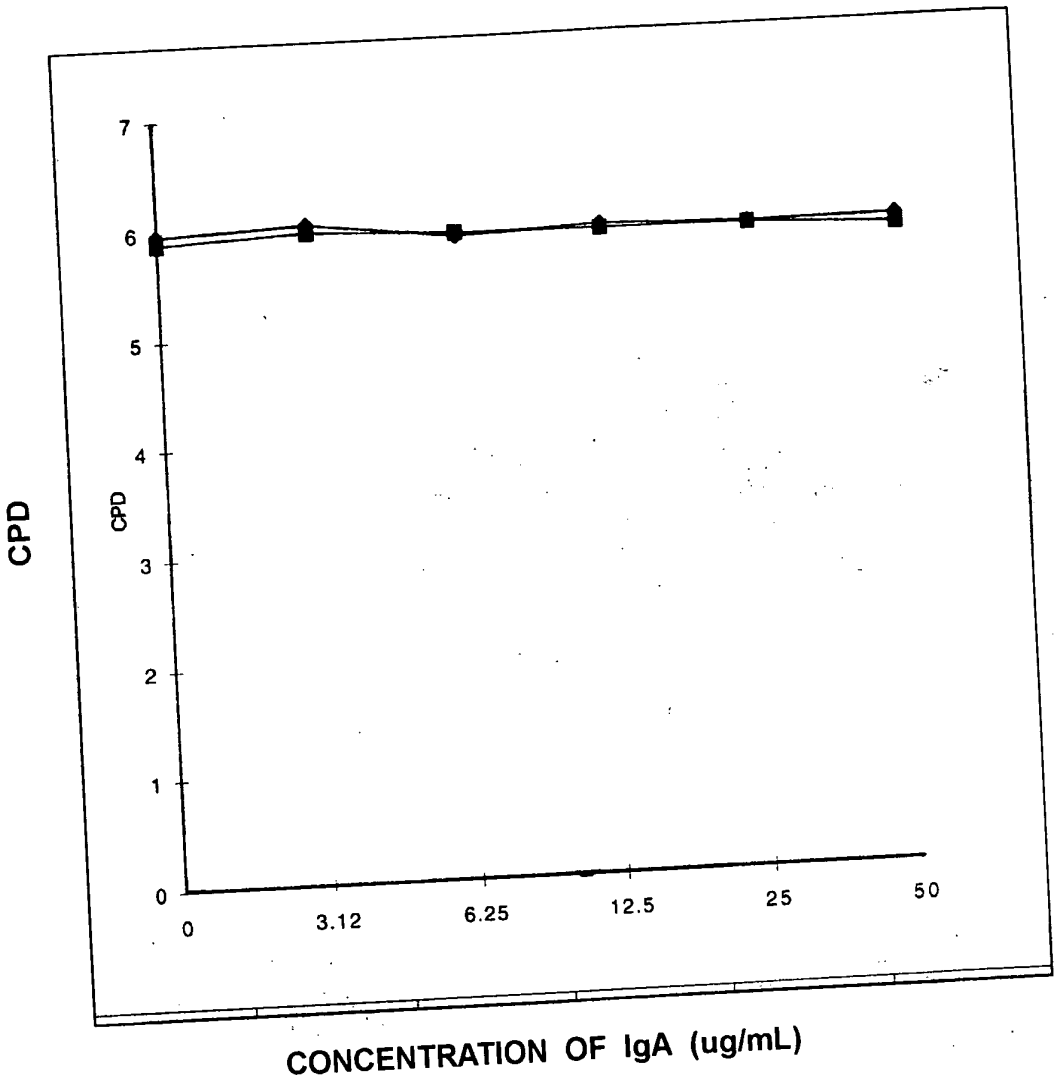


LEGEND:

1. MW
2. ALVA 41: 40 ug
3. ALVA 41: 20 ug
4. DU 145: 40 ug
5. DU 145: 20 ug
6. HUMAN FIBROBLAST: 40 ug
7. HUMAN FIBROBLAST: 20 ug
8. LNCaP: 40 ug
9. LNCaP: 20 ug
10. MDCK1: 20 ug
11. MDCK1: 10 ug
12. PC3: 40 ug

FIGURE 117

EFFECT OF HUMAN PLASMA IgA ON DU145 CELL GROWTH WITH AND WITHOUT DHT



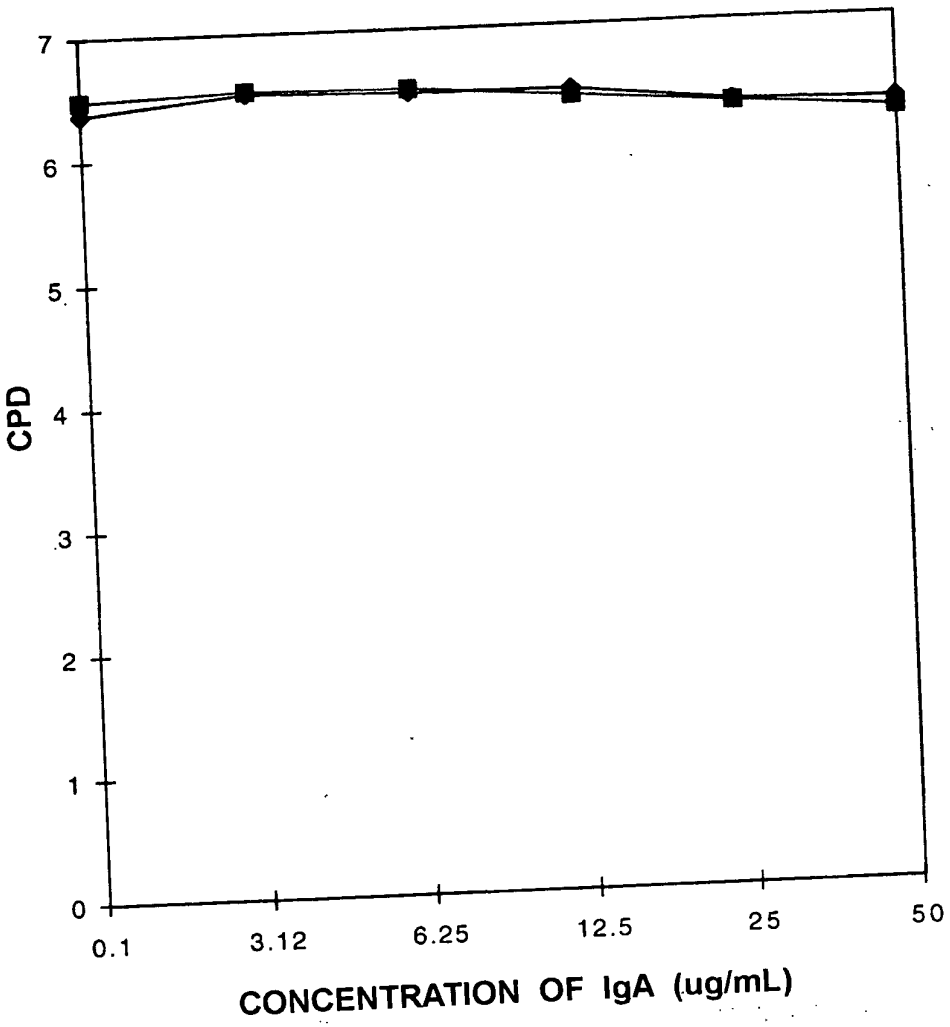
LEGEND:

= + DHT

= – DHT

FIGURE 118

EFFECT OF HUMAN PLASMA IgA ON PC3 CELL GROWTH WITH AND WITHOUT DHT



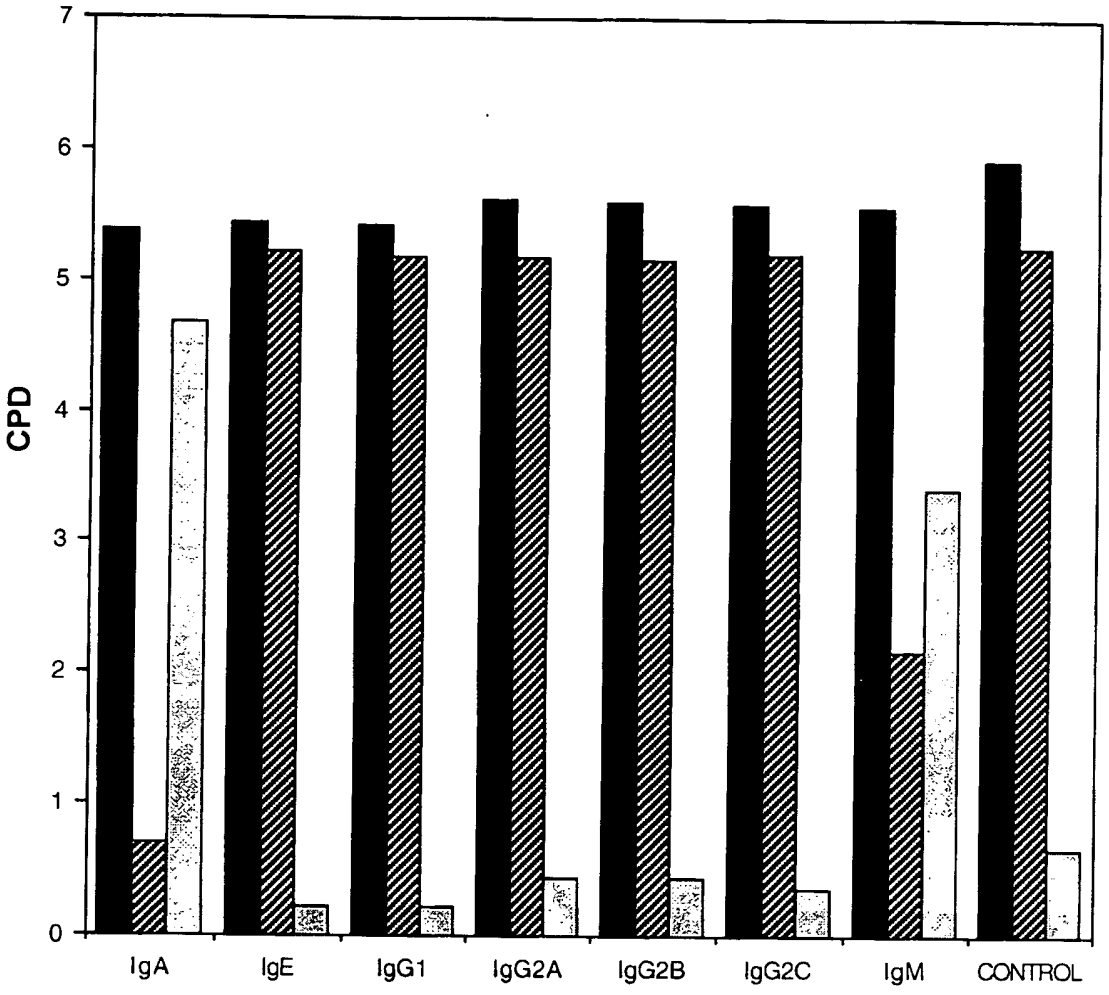
LEGEND:

= + DHT

= − DHT

FIGURE 119

EFFECT OF RAT IMMUNOGLOBULINS ON MTW9/PL2 CELL GROWTH IN SERUM-FREE MEDIUM



CONCENTRATION OF RAT IMMUNOGLOBULINS (15 ug/mL)

LEGEND:

■ = + E_2

▨ = − E_2

▣ = Estrogenic effect

CONTROL IS SERUM-FREE MEDIUM ALONE ± E_2

FIGURE 120

ESTROGENIC EFFECT GENERATED BY IMMUNOGLOBULINS WITH T47D CELLS IN SERUM-FREE MEDIUM

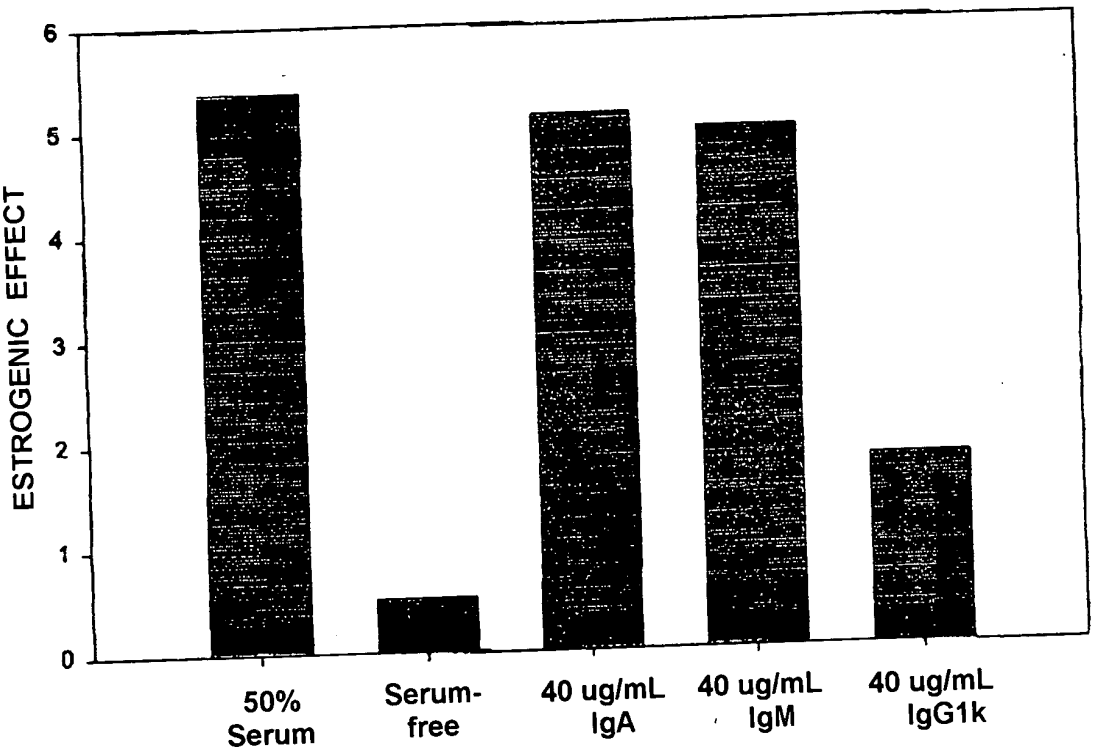
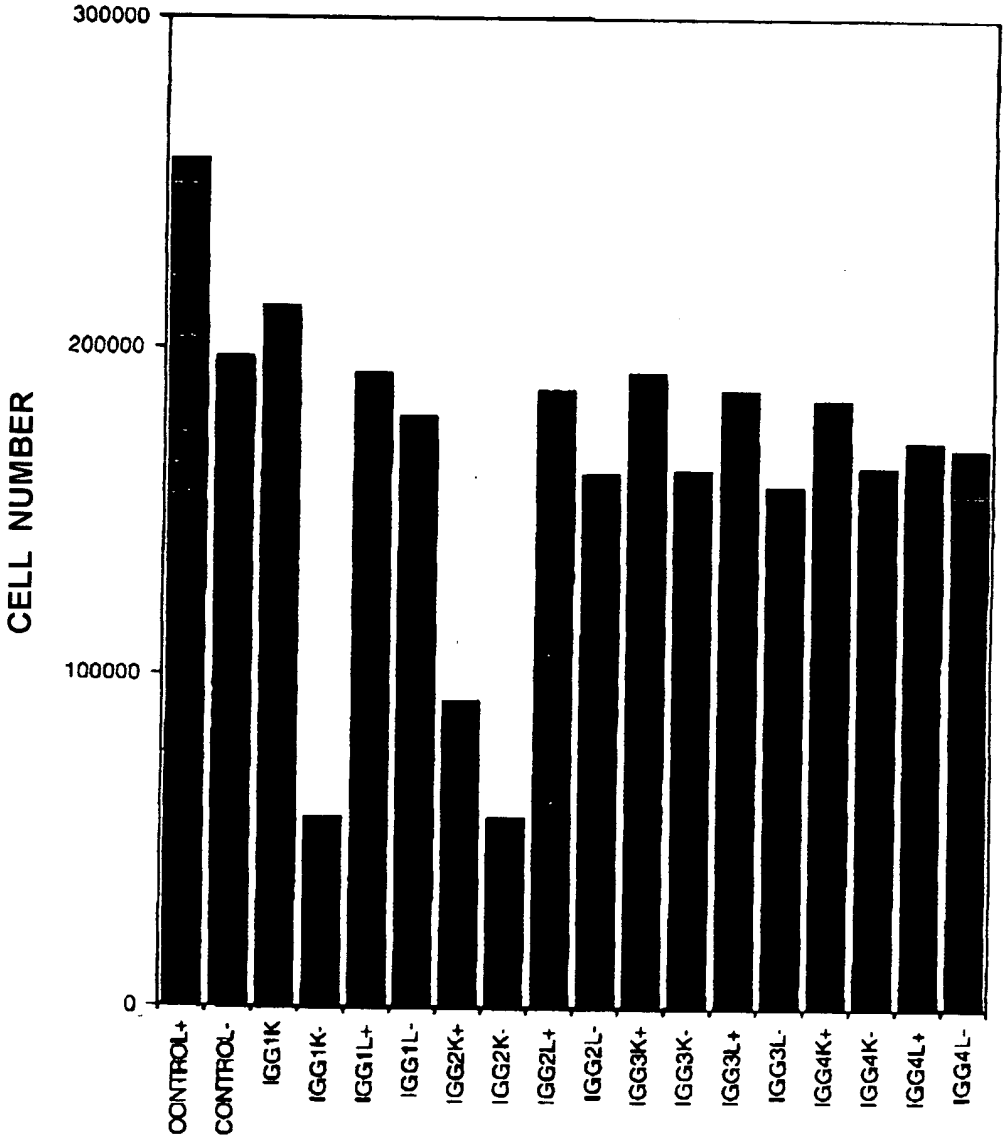


FIGURE 121

EFFECT OF IgG ISOTYPES (40 ug/mL) ON LNCaP CELL GROWTH IN SERUM-FREE MEDIUM



LEGEND: + = DHT Added
− = No DHT Added

FIGURE 122

IgG ISOTYPE ASSAYS WITH LNCaP CELLS IN SERUM-FREE DEFINED MEDIUM ± DHT

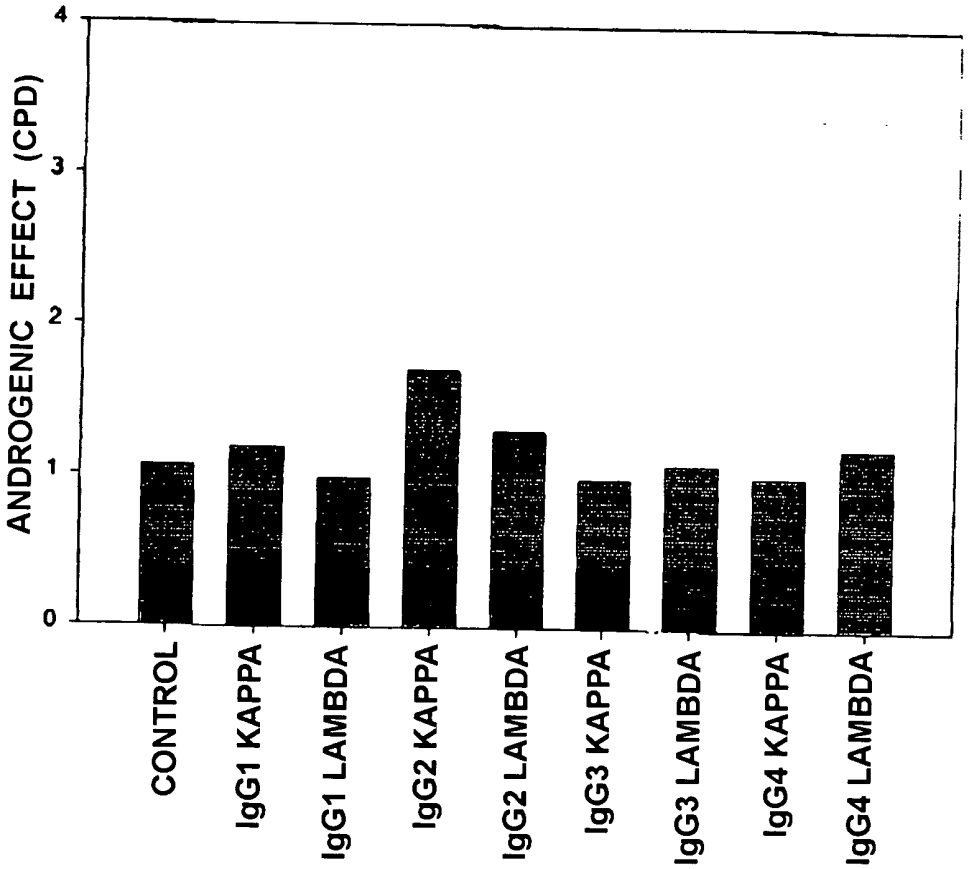


FIGURE 123

MODEL OF EARLY ONSET BREAST CANCER INCLUDING TGF-BETA

ER$^+$ BREAST CANCERS

(i) Inhibitory receptor(s) for IgA & IgM & IgG1

(ii) Growth inhibition by IgA & IgM

(iii) Little or no TGFβ growth inhibition

(iv) No TGFβ receptors

↗ ↗ ↗

NORMAL EPITHELIAL CELLS

I. Inhibitory receptor(s) for IgA & IgM & IgG1 & TGFβ

II. Growth inhibition by IgA & IgM & TGFβ

↘ ↘ ↘

ER$^-$ BREAST CANCERS

(i) No functional receptors for IgA or IgM & IgG1

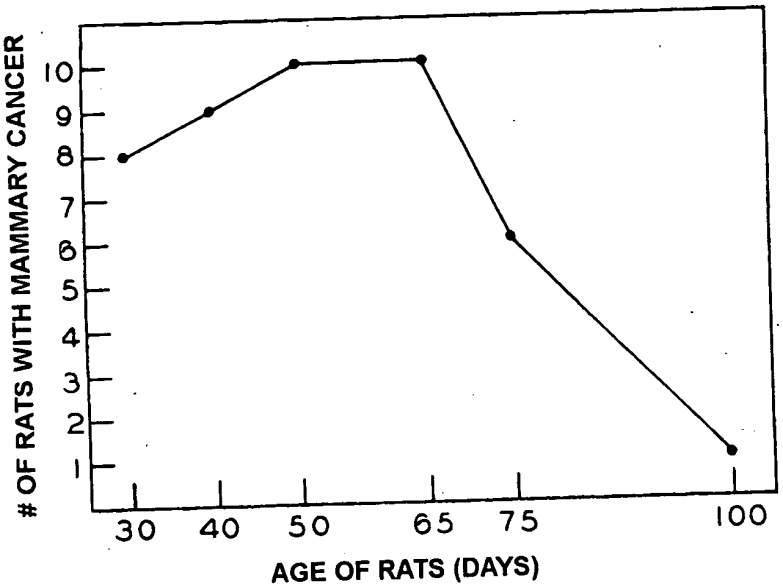
(ii) No growth inhibition by IgA & IgM

(iii) High sensitivity TGFβ growth inhibition

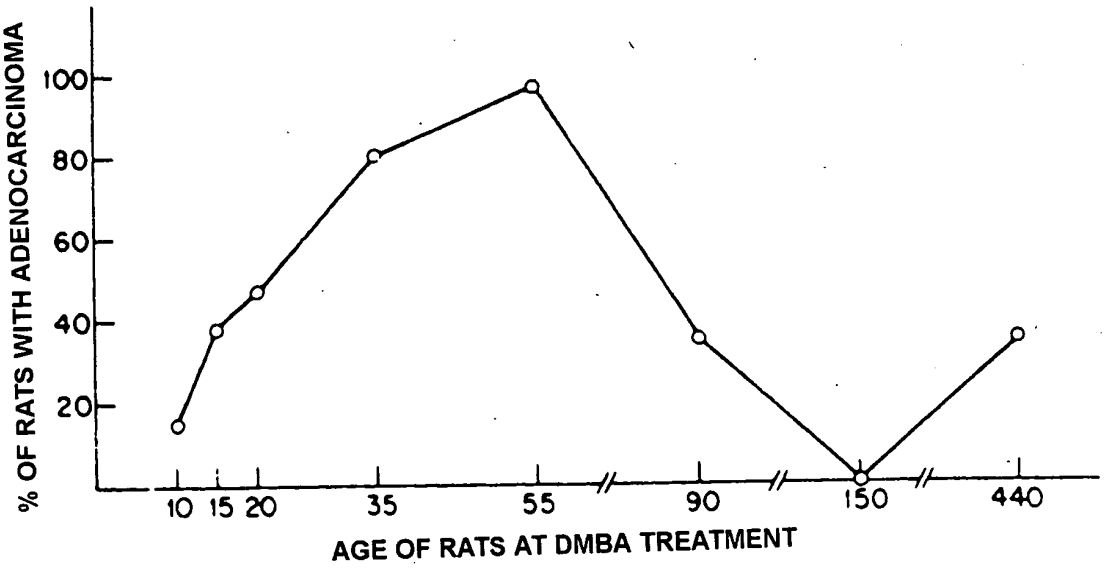
(iv) TGFβ receptors present

FIGURE 124

EFFECT OF CARCINOGENS ON MAMMARY TUMOR INDUCTION IN RATS OF VARIOUS AGES



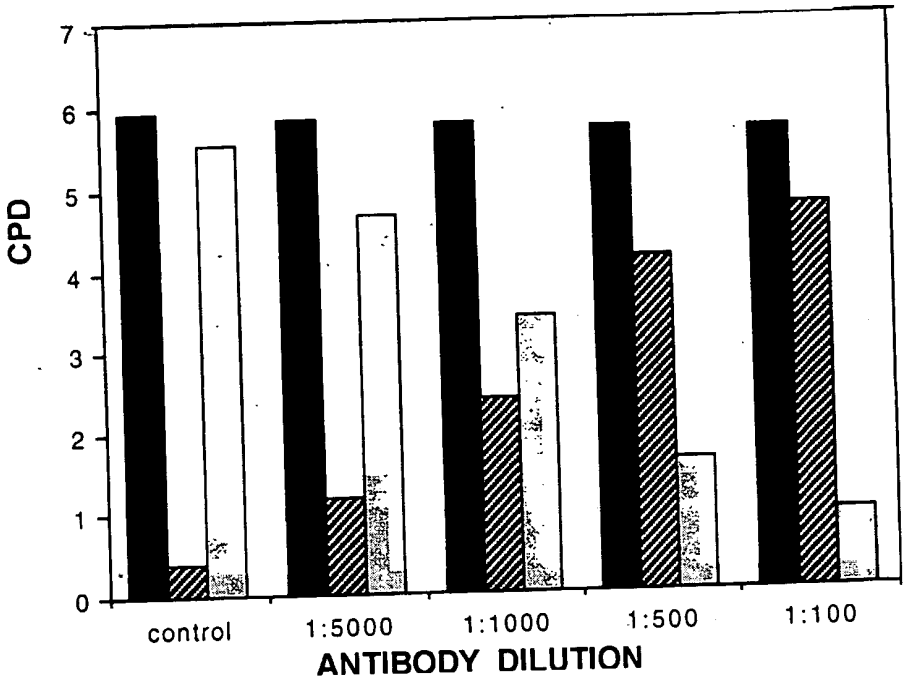
INCIDENCE OF MAMMARY CANCER IN GROUPS OF 10 FEMALE RATS OF VARIOUS AGES FED 3-MC, 100 MG



INCIDENCE OF MAMMARY ADENOCARCINOMA IN RATS GIVEN DMBA AT DIFFERENT AGES

FIGURE 125

ANTI-HUMAN SHBG ANTIBODY IMMUNOPRECIPITATION OF THE ESTROGENIC ACTIVITY PRESENT IN CDE-HORSE SERUM WITH MTW9/PL2 CELLS



LEGEND: ■ = GROWTH IN 50% CDE WITH E_2
▨ = GROWTH IN 50% WITHOUT E_2
▨ = E_2 EFFECT

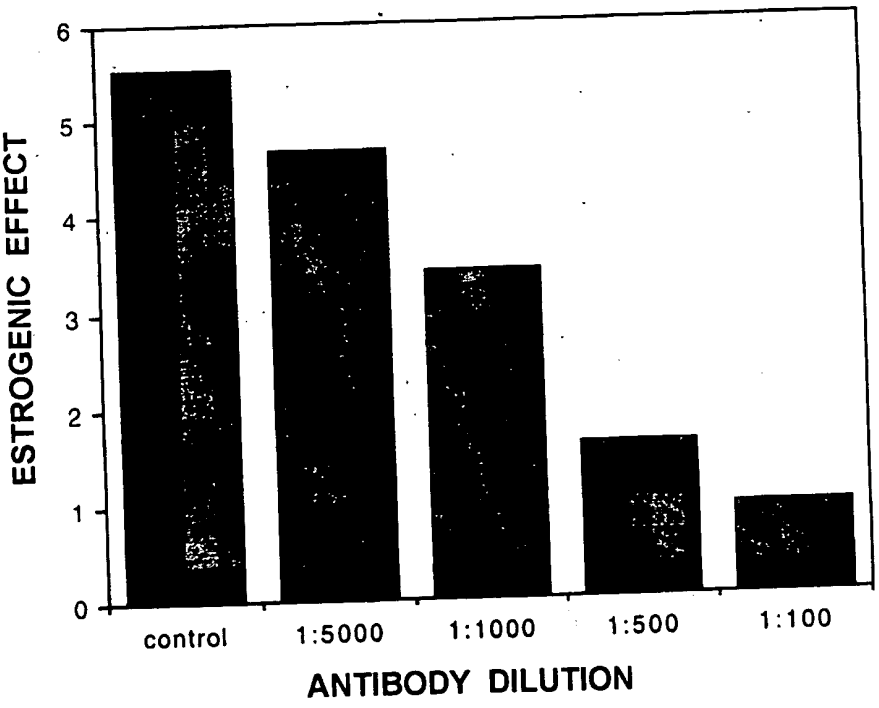
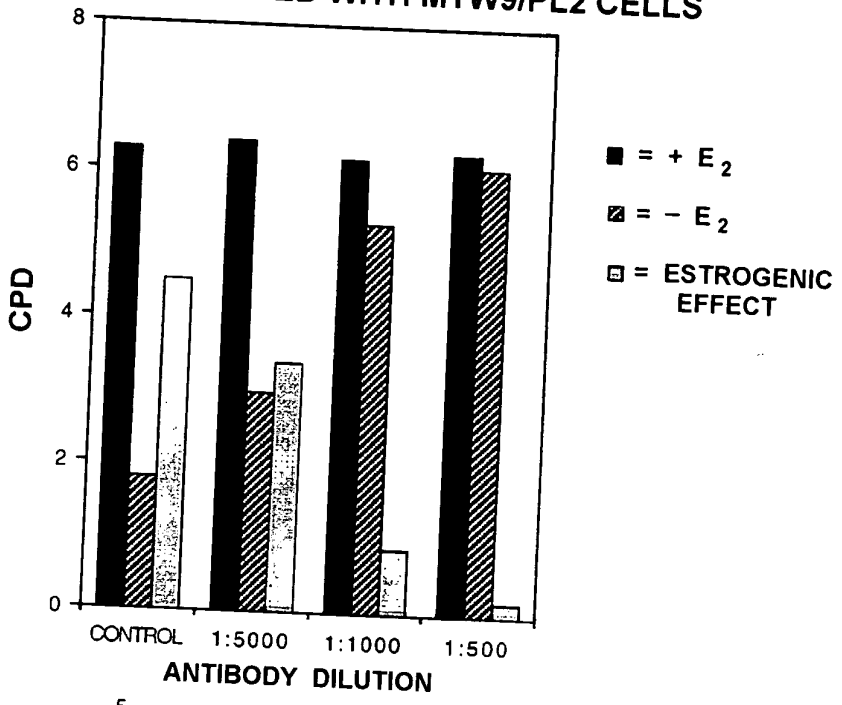


FIGURE 126

ANTI-HUMAN SHBG ANTIBODY IMMUNOPRECIPITATION OF THE ESTROGENIC ACTIVITY PRESENT IN CDE-RAT SERUM ASSAYED WITH MTW9/PL2 CELLS



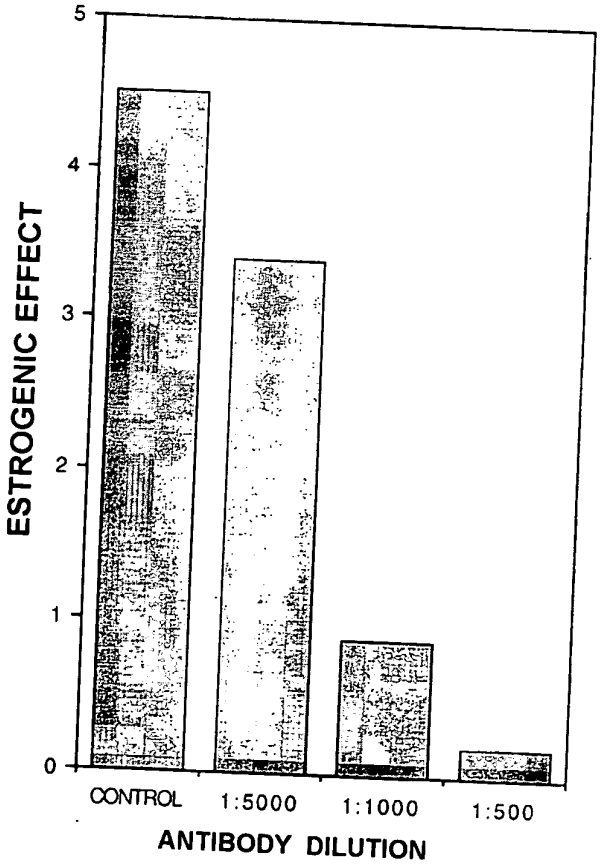


FIGURE 127

ANTI-HUMAN SHBG ANTIBODY IMMUNOPRECIPITATION OF THE LABELED STEROID HORMONE BINDING ACTIVITY PRESENT IN CDE-RAT SERUM

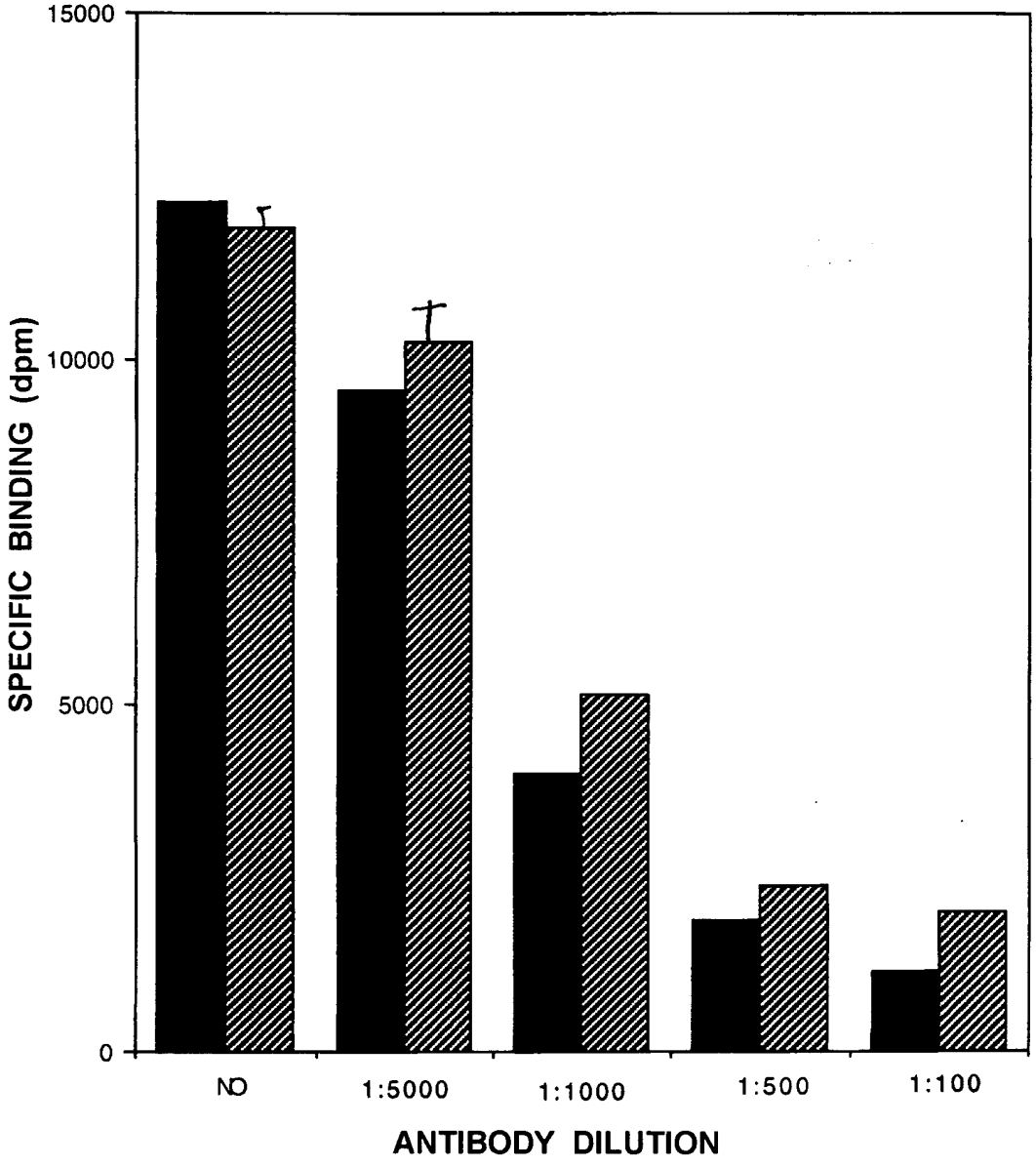
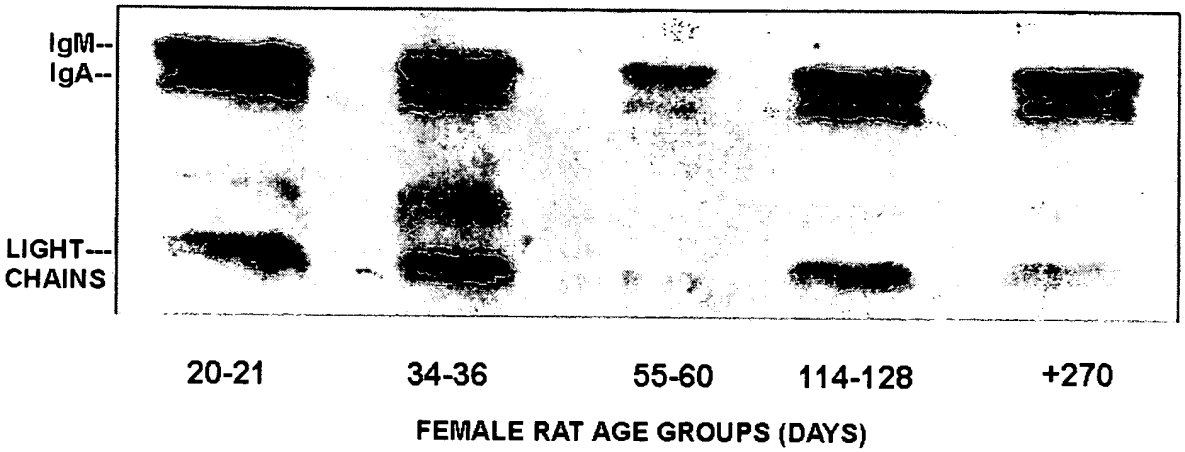


FIGURE 128

WESTERN ANALYSIS AND DENSITOMETRY OF THE IMMUNOGLOBULIN LEVELS IN THE SERUM OF FEMALE RATS OF SPECIFIED AGE GROUPS



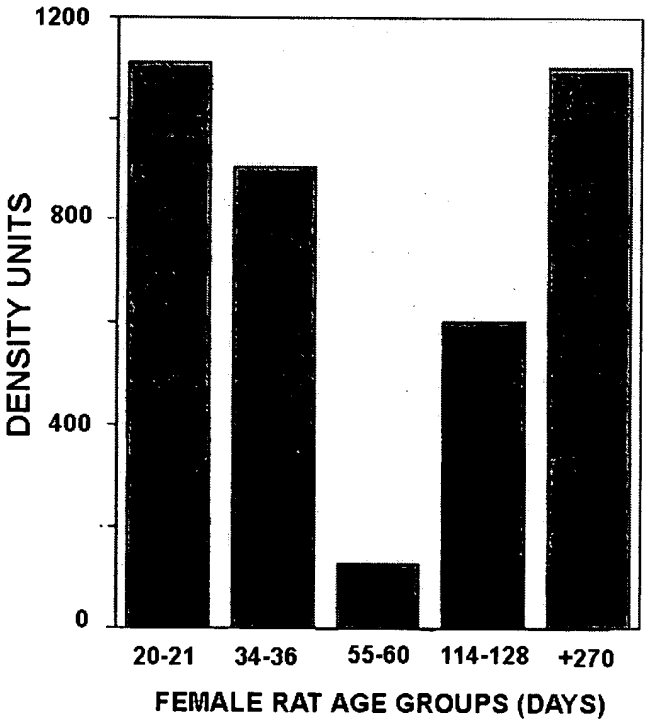


FIGURE 129

STRUCTURAL AND FUNCTIONAL ORGANIZATION OF THE HUMAN ESTROGEN RECEPTOR-alpha

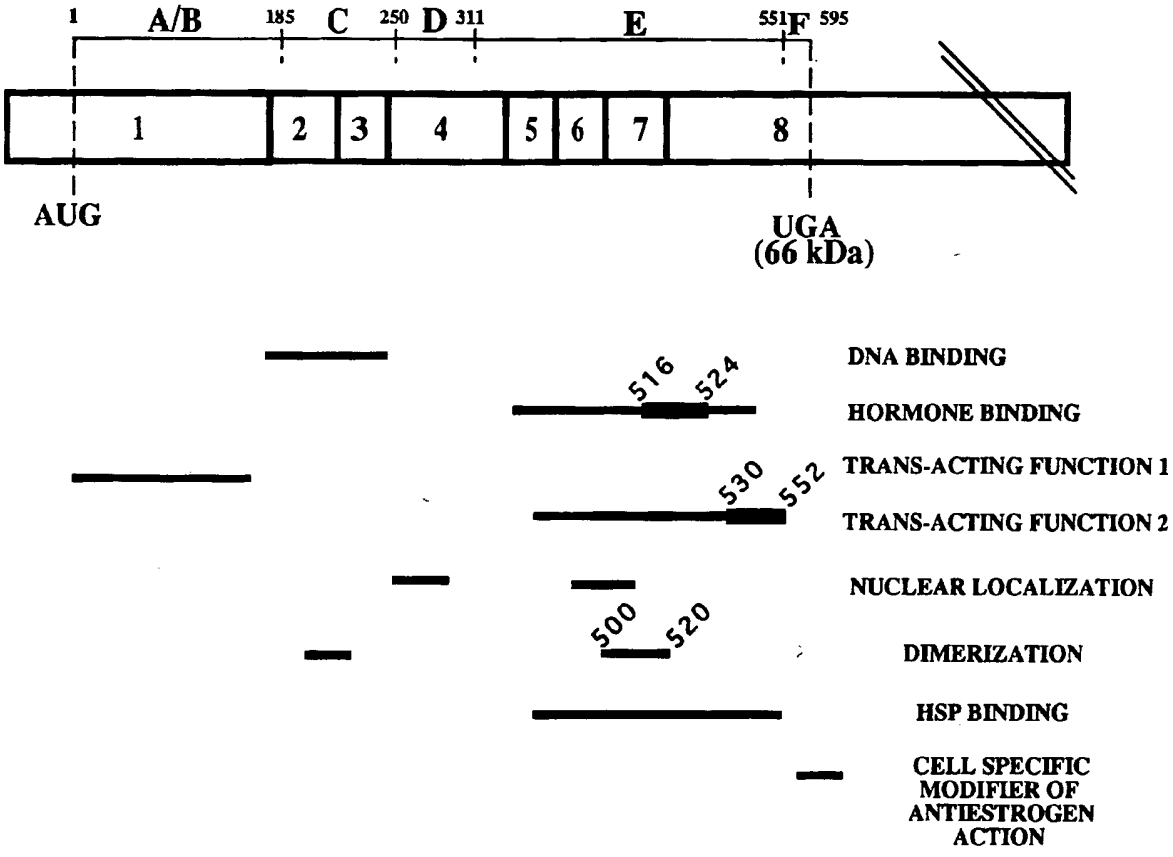
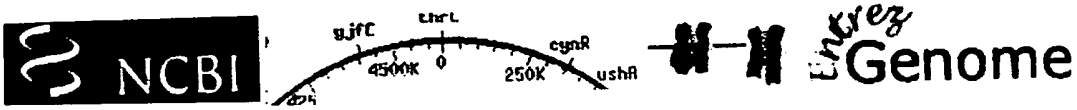
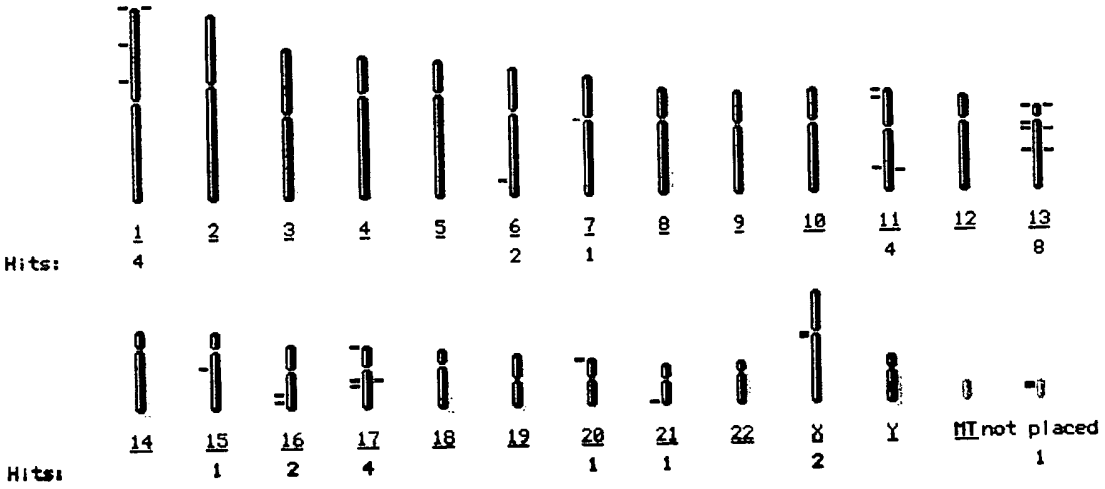


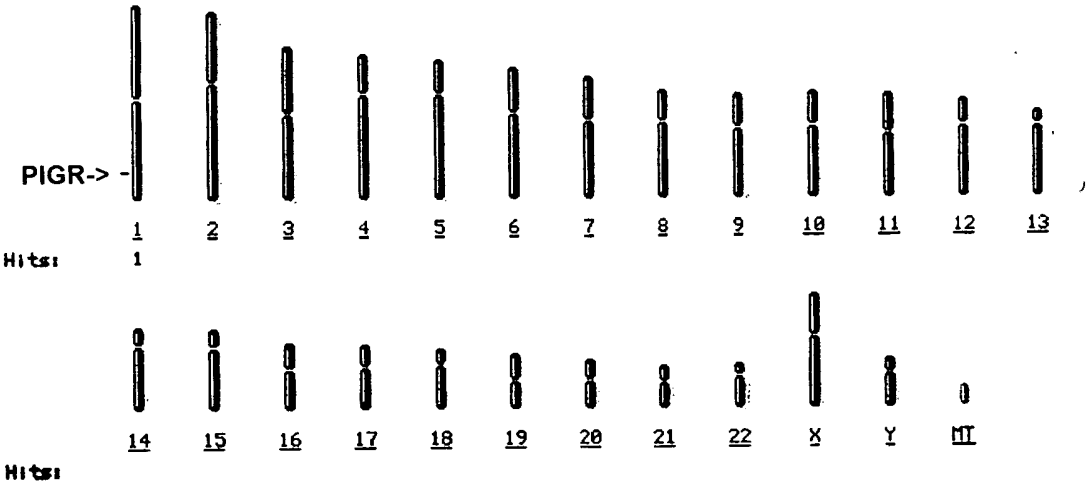
FIGURE 130



"BREAST CANCER" SEARCH - 31 "HITS"



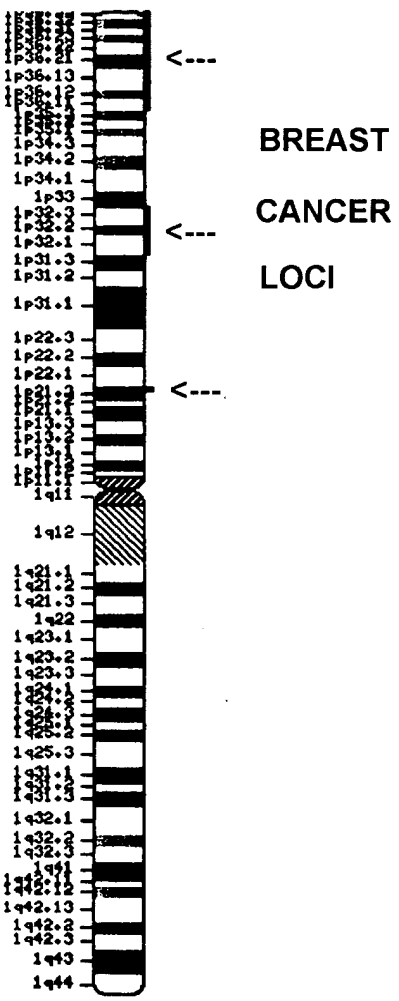
"PIGR" (POLY-Ig RECEPTOR) SEARCH - 1 "HIT"



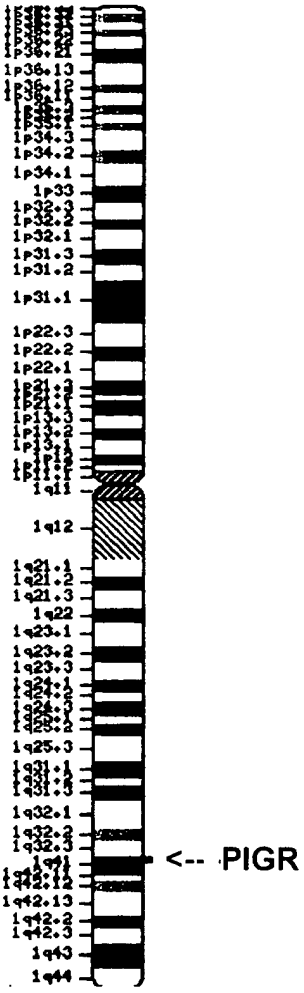
NOTE: THERE ARE NO BREAST CANCER "HITS" IN THE AREA OF THE POLY-Ig RECEPTOR ON CHROMOSOME 1

FIGURE 131

CHROMOSOME 1



BREAST CANCER SEARCH



PIGR SEARCH

FIGURE 132

CANCER AROUND THE WORLD, 1994-1997
DEATH RATES PER 100,000 (45 COUNTRIES)

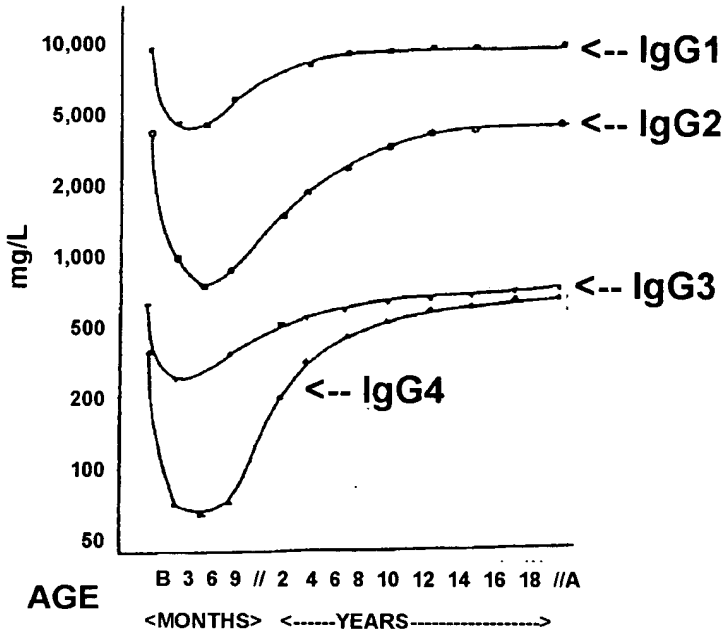
Country	Colon & Rectum		Breast	Prostate
	Male	Female	Female	Male
United States†	15.2 (27)	10.4 (23)	20.0 (14)	15.9 (20)
Australia‡	20.2 (10)	13.3 (10)	19.9 (15)	19.0 (9)
Austria†	21.7 (8)	12.2 (14)	20.9 (13)	16.9 (14)
Azerbaijan§	6.0 (41)	4.2 (43)	8.6 (42)	5.1 (41)
Bulgaria^	17.2 (20)	11.4 (19)	15.9 (31)	8.5 (34)
Canada‡	16.1 (26)	10.3 (25)	21.5 (10)	16.4 (17)
Chile^	7.0 (38)	6.7 (36)	12.1 (35)	16.0 (19)
China¶^	7.9 (36)	6.4 (37)	5.0 (44)	—
Colombia^	4.8 (44)	5.1 (40)	9.1 (40)	12.6 (28)
Croatia#	22.5 (6)	11.5 (18)	18.5 (20)	13.0 (25)
Cuba‡	9.4 (34)	11.3 (20)	14.9 (33)	20.8 (4)
Czech Republic§	34.3 (1)	17.3 (3)	21.1 (12)	16.0 (18)
Denmark§	22.7 (5)	15.6 (4)	27.6 (1)	19.9 (6)
Estonia§	18.1 (16)	12.2 (13)	18.5 (19)	12.8 (27)
Finland‡	12.1 (31)	8.5 (31)	16.8 (25)	17.6 (12)
France‡	16.6 (22)	9.6 (29)	19.6 (16)	15.8 (21)
Germany†	20.8 (9)	14.0 (7)	21.7 (8)	16.6 (16)
Greece§	8.0 (35)	6.2 (38)	16.2 (27)	9.3 (33)
Hungary^^	34.3 (2)	18.7 (2)	23.7 (6)	18.7 (11)
Ireland‡	22.5 (7)	13.3 (9)	26.1 (2)	18.8 (10)
Israel§	17.9 (18)	13.8 (8)	25.1 (4)	12.0 (30)
Japan**	17.1 (21)	9.9 (28)	7.7 (43)	5.1 (42)
Kazakhstan§	12.6 (30)	8.6 (30)	13.2 (34)	5.7 (39)
Kyrgyzstan§	6.9 (39)	4.5 (41)	10.6 (37)	4.3 (43)
Latvia‡	18.3 (12)	11.8 (15)	17.3 (24)	11.5 (31)
Lithuania§	18.2 (13)	11.7 (16)	18.7 (18)	15.2 (22)
Macedonia§	10.8 (33)	7.1 (34)	16.1 (30)	6.2 (38)
Mauritius§	6.0 (42)	3.8 (44)	9.0 (41)	7.7 (36)
Mexico‡	3.6 (45)	3.3 (45)	9.3 (39)	12.8 (26)
Netherlands‡	17.7 (19)	12.7 (11)	26.0 (3)	19.4 (8)
New Zealand^	26.4 (3)	19.1 (1)	22.9 (7)	19.8 (7)
Norway‡	20.0 (11)	14.7 (5)	19.4 (17)	23.2 (2)
Poland§	16.4 (23)	11.0 (22)	16.1 (29)	11.1 (32)
Portugal§	18.1 (15)	10.4 (24)	17.6 (22)	17.2 (13)
Rep. of Moldova‡	16.2 (25)	11.1 (21)	18.2 (21)	5.7 (40)
Romania§	11.3 (32)	7.9 (33)	15.7 (32)	8.3 (35)
Russian Fed.‡	18.2 (14)	12.6 (12)	16.1 (28)	7.2 (37)
Slovakia‡	14.6 (28)	6.8 (35)	—	12.2 (29)
Slovenia§	23.9 (4)	14.0 (6)	21.2 (11)	14.7 (23)
Spain‡	16.4 (24)	10.0 (27)	17.5 (23)	13.9 (24)
Sweden§	13.8 (29)	10.2 (26)	16.8 (26)	21.4 (3)
Trinidad & Tobago^	7.8 (37)	8.3 (32)	21.5 (9)	35.5 (1)
Turkmenistan^	6.2 (40)	4.4 (42)	9.5 (38)	1.4 (44)
United Kingdom†	18.0 (17)	11.6 (17)	24.5 (5)	16.6 (15)
Venezuela^	5.9 (43)	6.2 (39)	11.8 (36)	20.3 (5)

FIGURES IN PARENTHESES ARE ORDER OF RANK WITHIN SITE AND SEX GROUP

SOURCE: MORTALITY DATABASE 1994-97 WORLD HEALTH ORGANIZATION, 1999

FIGURE 133

A: TYPICAL CONCENTRATIONS OF IgG SUBCLASSES DURING CHILDHOOD



B: IMMUNOGLOBULIN CHANGES WITH AGE